**University of Alberta**

# Chemosensory Dysfunction in Advanced Cancer Patients

By

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## Abstract

This research expands the knowledge of chemosensory dysfunction in advanced cancer patients. A comprehensive set of objective clinical chemosensory tests were compared to self-assessment of taste and smell function (n=31). Self-perception of chemosensory function is materially different from that quantified by clinical tests. Although many patients report an increased perception of taste and smell, clinical tests reveal a loss of function. Dietary patterns were then related to pain and symptom profiles, with specific attention on chemosensory function (n=151). A large proportion of patients (88%) follow dietary patterns based on normal foods; however a small group (12%) consume a largely liquid diet. Patients consuming this liquid diet have greater chemosensory alterations, lower nutrient intakes, higher symptom distress, and are closer to death. Taste and smell alterations are prevalent in advanced cancer and deserve more attention in oncology research and management.

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# Chapter One

## Introduction

The chemical senses of taste and smell contribute to safety and quality of life in humans. Enjoying the flavour of food motivates us to eat, where as smelling gas or smoke serves as a warning of danger. Normal taste and smell function involves the interaction between chemical stimuli, nerve impulses and brain function. The physiological processes of "normal" taste and smell function have been recently reviewed in detail in the Handbook of Olfaction and Gustation (1).

Taste and smell disorders are often neglected because they are not seen as life-threatening or severe handicaps. However, severe chemosensory disorders pose a danger to health when food intake is substantially inhibited. Taste and smell dysfunction will affect food enjoyment, disrupt the cycle of food preparation and consumption in the family and decrease quality of life (QOL). There are a wide variety of causes for chemosensory dysfunction in humans. Taste and/or smell disorders can result from oral, perioral, nasal, or sinus diseases, upper respiratory tract infections, head trauma, medications, and aging (2). Cancer and its treatments are well known causes of taste and smell dysfunction; however chemosensory perception in patients with cancer has not been well documented.

Cancer patients are infrequently asked to describe their taste and smell disorders and clinical assessments are rarely made. Yet when studied, these disorders are reported to be common and distressing symptoms of cancer and its treatments. Individualized nutrition counselling and advice to accommodate chemosensory changes can improve the

nutritional intake of cancer patients (3). However, much of our current understanding of altered taste and smell perception in cancer is based on studies conducted more than twenty five years ago. The tips to combat this problem were developed from taste testing carried out in the 1970s and 80s and anecdotal information. Since this time methods for chemosensory testing have improved significantly. The development of standardized olfactory tests has allowed researchers to define the chemosensory abnormalities seen in HIV/AIDS (4-6), the elderly (7-15), and Alzheimer's disease (16-19). For the elderly, knowledge of taste and smell decline has resulted in dietary modifications which can increase food intake, immune function, and grip strength in retirement-home residents (20). The application of modern chemosensory testing techniques in cancer patients has been limited, especially in advanced cancer patients nearing the end of their life.

Chemosensory research in oncology patients rarely frames the results within the context of the overall cancer experience. The relationship between chemosensory changes and dietary intake has not been clearly established and the loss of food enjoyment that is a consequence of chemosensory alterations may compound other detriments to quality of life. Chemosensory testing should be combined with food intake measures, quality of life assessments, and symptom burden information to increase our appreciation of the importance of taste and smell changes for cancer patients.

**Taste and Smell Perception of Cancer Patients**

Changes in the taste and smell perception of cancer patients are related to a number of factors including cancer treatments, and metabolic deficiencies (21). Chemotherapy drugs

target rapidly proliferating cells, like those of the olfactory and gustatory systems, leading to damage and loss of perception (22). Patients may also experience a bitter or metallic taste during the administration of chemotherapy drugs (22). It is possible the medication is transferred to saliva and sensed by the patient when it reaches the oral cavity (22). Radiation destroys the replicating cells of the chemical senses when applied to the head and neck region leading to a loss of taste or smell function (23). Both radiation and chemotherapy can lead to learned food aversions (24). For example, patients may avoid certain foods or food odours that they associate with nausea or vomiting caused by cancer treatments. This could limit patients' nutrient intake if they avoid food high in protein such as meat, a common food aversion (25). Chemosensory dysfunction caused by cancer treatment may recover over time, however alterations can persist if regeneration of receptor cells and nerve fibres is incomplete or disturbed (25).

Studies indicate that chemosensory changes are a widespread problem in a variety of cancer populations. Many previous researchers report only the presence or absence of chemosensory symptoms as reported by cancer patients. Researchers have reported the prevalence of taste and occasionally smell changes based on responses to a single question on a symptom questionnaire (26-42). Other authors have used taste and smell questionnaires to evaluate chemosensory changes in more detail (Table 1.1) (43-51). Between 26 and 86 % of advanced cancer patients report taste changes and between ten and 56% report smell changes (27,29,34,36,40,43,46,50). The authors of these studies have recognized the importance of the chemical senses to quality of life for patients.

Table 1.1: Results of self-perceived chemosensory studies in cancer patients

| Authors | Participants | Method | Results |
|---|---|---|---|
| Bernhardson et al. (43) | 518 cancer patients treated with chemotherapy | Taste and smell questionnaire (33 questions) | 75% of patients reported tastea and smell changes |
| Buckingham et al. (26) | 11 ovarian cancer patients treated with surgery then carboplatin | 75-item self-report questionnaire of side-effects (WCQ-75) | 57% of patients reported taste changes. |
| Curtis et al. (27) | 100 advanced cancer patients | Standard tool with questions regarding 38 specific symptoms | 26% of patients reported taste changes. |
| Dodd (28) | 48 palliative cancer patients treated with chemotherapy | Chemotherapy Knowledge Questionnaire assessing 44 side effect of chemotherapy | 71% of patients reported taste and smell changes |
| Donelly et al. (29) | 1000 advanced cancer patients | Questionnaire assessing 38 symptoms | 28% of patients reported taste changes<br>13% found taste changes to be moderate or severe |
| Epstein et al. (30) | 20 head and neck cancer patients treated with radiation | EORTC QLQ-C30 with oral symptom and function scale | 90% of patients reported taste changes at the 6 month follow-up |
| Fanning & Hilgers (31) | 32 advanced ovarian cancer patients treated with surgery then high dose cisplatin and carboplatin | Gynecologic Oncology Group criteria for toxicity | 50% of patients reported taste changes. |
| Foltz et al. (32) | 59 cancer patients treated with chemotherapy as inpatients | Nail Self-Care Diary (SCD) | 66% of patients reported taste changes |
| Gift et al. (33) | 112 newly diagnosed lung cancer patients | Physical Symptom Experience tool assessing 37 common cancer symptoms | Early stage- 21% of patients report taste changes at diagnosis, 16% at 3 months, 12% at 6 months<br>Late stage- 45% of patients reported taste changes at diagnosis, 35% at 3 months, 31% at 6 months |
| Grosvenor et al. (34) | 254 advanced cancer patients | Standardized questionnaire of symptoms that influence weight loss | 46% of patients reported taste changes<br>Taste changes were related to weight loss |
| Harris & Griffin (44) | 99 gastrointestinal cancer patients treated with surgery | Postal questionnaire about taste and smell function (3 questions) | 45% of patients reported a taste or smell loss (80% taste only, 18% both, 1 patient only smell).<br>67% of pts fully recovered, all the rest (except 1) had partial recovery |

| Authors | Participants | Method | Results |
|---|---|---|---|
| Harrison et al. (35) | 29 tongue cancer patients<br>3 years after radiation treatment | Memorial Symptom Assessment Scale, Performance Status Scale for H&N Cancer | 34% of patients continued to experience taste changes, 70% of these patients found this symptom to be moderate or severe |
| Huldij et al. (45) | 28 women with endometrial/cervical cancer, 52 men with bladder/prostate cancer, 28 men & women with lymphoma | Subjective questionnaire regarding appreciation of basic tastes and foods | Patients had a decreased appreciation for bitter taste and boiled fish after radiation and/or chemotherapy |
| Hutton et al. (46) | 66 advanced cancer patients | Taste and Smell Survey (14 questions) | 52% of patients reported both taste and smell changes<br>30% of patients reported only taste changes<br>5% of patients reported only smell changes |
| Komurcu et al. (36) | 50 advanced cancer patients | Survey interview assessing 17 gastrointestinal (GI) symptoms | 60% of patients reported taste changes |
| Kuten et al. (37) | 32 head and neck cancer patients treated with radiation | Complaints were recorded including taste impairment | 62% of patients reported taste impairment |
| Lees (38) | 100 head and neck cancer patients prior to treatment | Questionnaire assessing 9 nutrition related symptoms | 28% of patients reported taste changes, 20% had a loss of taste, 19% experienced a metallic taste, 5% experienced an unpleasant taste |
| Lindley et al. (39) | 146 cancer patients treated with chemotherapy | Category scales assessing perceived magnitude of 41 chemotherapy side effects. | 46% of patients reported taste changes, 35% of patients reported smell changes, These symptoms bothered them "quite a bit" or "very much" |
| McDaniel et al. (47) | 20 breast cancer patients receiving Tamoxifen | Sensory Information Questionnaire (open ended & focused questions about all 5 senses) | 75% of patients reported taste changes, 55% of patients reported smell changes. Patients used self-care coping rather than asking the doctor |
| Rhodes et al. (48) | 44 cancer patients starting chemotherapy | Sensory Information Questionnaire (open ended & focused questions about all 5 senses) | 77% of patients reported taste changes<br>64% of patients reported smell changes |
| Sarhill et al. (40) | 352 advanced cancer patients | Standardized gastrointestinal symptom questionnaire | 16% of patients had an abnormal metallic taste<br>16% of patients reported decreased taste function<br>7% of patients reported increased taste sensitivity<br>10% of patients reported decreased smell function |

| Authors | Participants | Method | Results |
|---|---|---|---|
| Sitzia et al. (41) | 19 non-hodgkin's lymphoma patients treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) | 75-item self-report questionnaire of side-effects (WCQ-75) | 74% of patients reported taste changes (3rd most common and troublesome symptom)<br>Severity increased over the course of treatment |
| Stubbs (49) | 218 solid tumour cancer patients | List of 25 foods & drinks; patients rated if they tasted better, worse, or the same | 25% of patients reported taste changes<br>Foods associated with taste change were meat, eggs, coffee, and tea |
| Walsh et al. (50) | 25 advanced cancer patients in hospice | Interviewed using a structured questionnaire | 52% of patients reported taste changes<br>Patients had a change in food preferences for sweet foods and meats |
| Wickman et al. (51) | 284 cancer patients treated with chemotherapy | 41-item subjective taste change questionnaire and FACT-G quality of life questionnaire | 68% of patients reported taste changes, 38% found taste changes to be moderate to severe.<br>Taste changes associated with decreased quality of life |
| Yan & Sellick (42) | 146 newly diagnosed gastrointestinal cancer patients | Self-report questionnaire assessing symptoms and quality of life | 11.6% of patients reported taste changes. 41.8% of patients report that food is unappealing. Taste changes have the highest severity rating and second highest distress rating of all symptoms. |

However, chemosensory disorders are not given the same attention as other symptoms such as pain or nausea in current cancer care. Unfortunately there are no well-accepted interventions to overcome the chemosensory alterations in cancer, making them difficult to manage.

To date, almost all published accounts of chemosensory function in cancer patients used isolated clinical tests of a single facet of taste or smell function. Taste thresholds, taste perception, and smell function were each evaluated in isolation. Taste thresholds have been evaluated in cancer patients with varying results (Table 1.2) (52-74). Although past studies reveal that taste function is affected by cancer and/or its treatments, there is no agreement on which tastes are affected and in which way. This inconsistency may reflect the variety of cancer populations studied, including different cancer types, stages, and treatment protocols, and the different methods for selecting control subjects (60,66). In addition, the methods used for threshold testing are outdated and few researchers have used current standard methods of taste threshold testing (75). Measuring mean taste thresholds assumes that cancer patients will have an increased or decreased sensitivity for the basic tastes. This ignores the large number of cancer patients who report an altered or distorted taste experience (46).

There is a lack of research in the area of smell dysfunction, particularly in advanced cancer patients (Table 1.3) (67,76-86). Although standardized methods for olfactory testing are widely available, the majority of studies assessing smell function in cancer

Table 1.2: Results of taste threshold testing in cancer patients

| | | | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Detection Thresholds | | | | Recognition Thresholds | | | |
| **Authors** | **Participants** | **Threshold Method** | **Sweet** | **Sour** | **Salty** | **Bitter** | **Sweet** | **Sour** | **Salty** | **Bitter** |
| Bertertche et al. (52) | 110 cancer patients treated with chemotherapy, 170 controls | Electrogustometer | ↑ | | | | \ | \ | \ | \ |
| Bolze et al. (53) | 35 cancer patients treated with radiation, 13 controls | 3-stimulus drop | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| Bruera et al. (54) | 36 advanced cancer patients treated with chemotherapy, 18 controls | Whole mouth | \ | \ | \ | \ | ↑ | \ | \ | \ |
| Carson & Gormican (55) | 29 breast cancer patients and 19 colon cancer patients, 28 controls | 3-stimulus drop | ↑ | ↔ | ↑ | ↔ | ↑ | ↔ | ↑ | ↔ |
| Conger (56) | 9 head and neck cancer patients | Whole mouth | \ | \ | \ | \ | ↑ | ↑ | \ | ↑ |
| DeWys & Walters (57) | 50 metastatic cancer patients 23 controls | 3-stimulus drop | ↑ | ↑ | ↔ | ↔ | ↑ | ↔ | ↔ | ↓ |
| Gallagher & Tweedle (58) | 50 cancer patients prior to treatment 50 controls | 3-stimulus drop | \ | \ | \ | \ | ↑ | ↔ | ↔ | ↓ |
| Hall et al. (59) | 30 gastrointestinal cancer patients 30 patients with benign GI disease 30 controls | 3-stimulus drop | \ | \ | \ | \ | ↔ | ↔ | ↔ | ↓ |
| Kamath et al. (60) | 12 esophageal cancer patients 14 controls | 3-stimulus drop | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ | ↔ |
| Marinone et al. (61) | 15 allogeneic bone marrow transplant patients, 8 autologous bone marrow transplant patients, 20 controls | Whole mouth | \ | \ | \ | \ | ↔ | ↑ | ↑ | ↔ |
| Mattson et al. (62) | 26 patients treated with bone marrow transplant, 10 patients 2-5 years post transplant, 12 controls | Whole mouth | ↑ | ↑ | ↑ | ↑ | ↔ | ↑ | ↑ | ↑ |

| | | | Results | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Detection Thresholds | | | | Recognition Thresholds | | | |
| Author | Participants | Thershold Method | Sweet | Sour | Salty | Bitter | Sweet | Sour | Salty | Bitter |
| Minakata et al. (63) | Lung cancer case study patient | Electrogustometer | ↑ | | | | \ | \ | \ | \ |
| Mossman et al. (64) | 51 head and neck cancer patients treated with radiation | 3-stimulus drop | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| Mossman & Henkin (65) | 27 head and neck cancer patients treated with radiation | 3-stimulus drop | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| Ovesen et al. (66) | 27 small-cell lung cancer patients 24 controls | 3-stimulus drop | \ | \ | \ | \ | ↔ | ↔ | ↔ | ↔ |
| Ovesen et al. (67) | 28 lung, 17 ovarian, 6 breast cancer patients, 29 controls | Electrogustometer | ↑ | | | | \ | \ | \ | \ |
| Pattison et al. (68) | 42 advanced cancer patients 42 controls | Whole mouth | ↔ | ↔ | ↔ | ↓ | ↔ | ↔ | ↔ | ↓ |
| Ripamonti et al. (69) | 18 head and neck cancer patients treated with radiation | 3-stimulus drop | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| Sandow et al. (70) | 13 head and neck cancer patients treated with radiation | Whole mouth | ↑ | ↑ | ↑ | ↑ | \ | \ | \ | \ |
| Shi et al. (71) | 30 head and neck cancer patients treated with radiation | Whole mouth | \ | \ | \ | \ | ↔ | ↔ | ↔ | ↔ |
| Tomita & Osaki (72) | 41 oral cancer patients 100 controls | Filter-paper disc | \ | \ | \ | \ | ↑ | ↑ | ↑ | ↑ |
| Williams & Cohen (73) | 30 lung cancer patients 30 controls | 3-stimulus drop | \ | \ | \ | \ | ↔ | ↑ | ↔ | ↔ |
| Yamagata et al. (74) | 12 lung cancer patients treated with chemotherapy | Electrogustometer | ↑ | | | | \ | \ | \ | \ |

↑ indicates an increased taste threshold; ↓ indicates a decreased taste threshold; ↔ indicates unchanged threshold relative to controls; \ indicates that this test was not performed in the study

Table 1.3: Results of olfactory function testing in cancer patients

| Authors | Participants | Methods | Results |
|---|---|---|---|
| Fujii et al. (76) | 29 laryngectomy cancer patients | Jet Stream Olfactometer (detection & recognition odour thresholds) | Odour thresholds increased for 3 months after surgery, then they recover<br>**92.6%** of patients reported hyposmia |
| Henkin et al. (77) | 29 laryngectomy cancer patients | Odour thresholds (detection and recognition for several odours) | Normal smell function prior to surgery<br>Odour thresholds increased after surgery |
| Hilgers et al. (78) | 44 laryngectomy cancer patients | Odour discrimination test<br>Olfaction/Taste/Appetite Questionnaire | Patients taught the "polite yawning technique" to increase smell function, after intervention the number of smellers increased from 25% to 57% |
| Ho et al. (79) | 48 nasopharyngeal cancer patients treated with radiation | Sniffin' Sticks (threshold, identification, discrimination) | Odour threshold increased 12 months after RT, no difference in odour identification & discrimination ability |
| Holscher et al. (80) | 44 head and neck cancer patients treated with radiation. 22 of these patients received radiation to their olfactory epithelium | Sniffin' Sticks (threshold, identification, discrimination) | Odour discrimination ability declined for patient receiving RT to the olfactory epithelium 2 weeks into treatment |
| Hua et al. (81) | 25 nasopharyngeal cancer patients treated with radiation, 25 nasopharyngeal cancer patients waiting for radiation, 36 controls | Odour threshold, discrimination, and identification tests | Patients had lower smell function compared to controls. Patients treated with RT had lower smell function compared to patients waiting for RT |
| Lehrer et al. (82) | 46 breast cancer patients<br>46 controls from the University of Pennsylvania taste and smell centre data | UPSIT (odour identification) | Estrogen receptor + patients had lower UPSIT scores than controls, estrogen receptor - patients had similar scores to controls |
| Ophir et al. (83) | 12 nasopharyngeal or pituitary adenoma cancer patients treated with radiation | Amyl acetate and eugenol odour detection thresholds | Odour thresholds are increased by the end of radiation treatment, some recovery seen 3-6 month after RT, no patient had fully recovered |
| Ovesen et al. (67) | 28 lung, 17 ovarian, 6 breast cancer patients, 29 controls | Phenyl-methyl-ethyl carbinol odour detection threshold | No difference in smell thresholds between cancer patients and controls |
| van Dam et al. (84) | 63 laryngectomy cancer patients | Phenyl-ethyl-alcohol odour detection threshold<br>Odour discrimination test | 32% of patients were able to smell<br>Patients accurately judged their olfactory capability |
| Yakirevitch et al. (85) | 21 patients treated with cisplatin (combined with 5-FU, etoposide, or temozolomide) | Sniffin' Sticks (identification) | 1 patient (4.6%) showed decreased smell function |
| Yakirevitch et al. (86) | 42 advanced cancer patients in hospice | Sniffin' Sticks (identification) | 60% of patients had poor smell function |

patients have been in the head and neck population (79-81,83), focussing on patients having undergone a laryngectomy (76-78,84). Only one study has measured smell function specifically in patients with end-stage cancer. The researchers found that 60% of patients had a measurable smell dysfunction (86).

The approach of assessing a single aspect of chemosensory function provides limited information about chemosensory perception. Taste and smell are tightly linked in the perception of food flavour and should be studied together. It is common for people to mistake the flavour of a food as taste (87); however smell contributes the majority of food flavour. Therefore, most complaints of taste loss are actually the result of a smell dysfunction (88). Many patients are unable to accurately describe a change in their smell function and may not realize they have this problem. At taste and smell clinics a number of clinical tests are used to accurately diagnose chemosensory disorders including taste thresholds, smell thresholds, and odour identification (88). A comprehensive research approach is needed to assess patient perception of chemosensory ability as well as clinical taste and smell function. Further, patients should be grouped based on perceived or clinically-evaluated chemosensory loss or distortion to reveal the relationship between taste and smell function and clinical variables such as weight loss, nutrient intake, and symptom burden. Hutton et al have used this approach to highlight the association between perceived chemosensory dysfunction and poor dietary intake and QOL (46).

**Modern Chemosensory Testing Techniques**

The current sensory techniques to evaluate taste and smell function are based on methods endorsed by the International Standards Organisation (ISO) and the American Society for Testing and Materials (ASTM). The methods are grounded in psychophysics, a discipline of psychology that quantifies the relationship between physical stimuli and their perception (89).

***Taste Threshold***

Taste function is usually measured using a threshold technique. The detection threshold is the concentration at which the subject recognizes a taste solution to be different from water and the recognition threshold is the concentration at which the participant can identify the taste. The tastants used for testing are sucrose for sweet, sodium chloride for salty, citric acid for sour, and quinine or caffeine for bitter (90).

The most common technique used to assess taste function in cancer patients has been the "three-drop stimulus technique" (91) where small drops of solution are placed on the tongue; one drop of the tastant dissolved in water and two drops of filtered water. Although this technique was popular in the medical literature, the results depend on the location and number of taste buds stimulated by the drops (24). Thus it defines capabilities in a specific region of the tongue and is classified as "regional testing". Another procedure to measure taste thresholds is electrogustometry. In this technique an anode is used to apply an electrical stimulus to the tongue (92). Electrogustometry has been used with the cancer population (52,63,67,74), however a study of healthy young

and elderly participants suggests that this technique does not correlate well with chemical threshold taste testing (92). Although at higher concentrations this stimulus is described as having a metallic, salty, or sour taste (90), at threshold concentrations many participants describe a vibration or buzzing sensation, rather than a taste descriptor (92). It has been argued that the regional testing employed in these methods is more sensitive than whole mouth testing (93); however the results may not relate to the patients' experience with taste while eating.

The current ISO standard technique to measure taste detection and recognition thresholds uses whole mouth stimulation (75). In a two-alternative, forced-choice procedure subjects sample solutions from two cups, one contains the tastant and the other is water (90). An ascending method of limits or single staircase procedure is used to determine the threshold concentration. The ascending method of limits involves presenting the stimulus from weakest concentration to highest concentration until the subject makes a certain number of correct choices in a row (often three or five) (94). In the single staircase procedure the concentration is increased when the subject makes an incorrect choice and decreased when the subject makes a correct choice until a certain number of direction changes are made (for example the threshold may be the mean of the last four out of seven staircases reversals) (95).

***Smell Function***

A number of clinical tests are available to evaluate smell function in humans. These tests measure the olfactory capabilities of odour identification, odour detection threshold,

odour discrimination, or retronasal smell function. Several tests may be used together for a complete understanding of smell function. When evaluating smell function of patients with advanced cancer, patient burden should be considered and shorter test procedures used if possible.

***Odour Identification***

Odour identification requires the participant to name an odour stimulus (94). Odour naming can be difficult, even for those with normal smell function, so most tests involve cuing either through multiple choice options for each odour or a comprehensive list of odorants and distracters (94). The most common test used in North America is the University of Pennsylvania Smell Identification Test (UPSIT) which is commercially available as The Smell Identification Test™ from Sensonics, Inc (94). This tool includes four booklets with forty microencapsulated odour stimuli presented in a multiple choice, scratch 'n sniff format (95). Norms have been developed to classify patients as normosmic, hyposmic, or anosmic, and this test can detect olfactory dysfunction associated with age and many medical conditions (96).

A shorter version of the UPSIT, the Cross-Cultural Smell Identification Test, includes only twelve odours that are easily recognized by a wide variety of cultures (97). This test is commercially available as the Brief Smell Identification Test (B-SIT). Because this test involves fewer odours, it takes only five minutes to administer and limits olfactory fatigue. Although this test is slightly less sensitive than the UPSIT, it is a quick, reliable tool for assessing smell function.

Impaired performance on the UPSIT is due to olfactory dysfunction rather than cognitive decline. Moberg et al. (98) used the Picture Identification Test (PIT) (99), which is identical in format to the UPSIT, to demonstrate that Alzheimer's disease and Schizophrenia patients are able to perform an identification task. Olfactory recognition tests are routinely used to assess the onset and severity of Alzheimer's disease (16-19).

***Odour Threshold***

Measuring a subject's detection threshold determines the lowest concentration at which an odorant can be detected (94). Many standardized odour threshold procedures use 1-butanol as the odour stimulus because it has a low toxicity, is soluble in water, has a neutral odour quality, is readily accessible, and has served successfully in many olfactory experiments (100). The threshold procedure is similar to the two-alternative forced-choice procedure described above to determine taste thresholds. Two or more stimuli are presented, the odour and one or more blanks, and the participant must identify which is the odour (94). Both the ascending method of limits and the single staircase method can be used to determine the threshold concentration. The single staircase method has a better test-retest reliability compared to an ascending method of limits (96). However this procedure is lengthy and may result in fatigue in cancer patients.

It is useful to combine threshold testing with other olfactory tests to gain a complete understanding of smell function. Several tests used in research and chemosensory clinics throughout the world combine odour threshold and identification testing. One such

procedure is the Connecticut Chemosensory Clinical Research Center (CCCRC) test which combines a butanol odour threshold test with an odour identification test (101). The odour identification component of the CCCRC includes eight common odorants presented in opaque plastic jars which are identified from a list of sixteen items. Advantages of the CCCRC are that it is portable, inexpensive to make, and can be administered anywhere (101).

The "sniffin' sticks" is a European commercially available set of tests that uses felt-tip pens as odour dispensers (102) for odour identification, odour discrimination and odour threshold evaluation. Odour identification is assessed using sixteen odours in a four-item multiple choice format. Odour discrimination ability is determined through a triplet presentation where the patient chooses the odd sample in each of sixteen different triplets. Finally, odour threshold is determined by a three-alternative, forced-choice single staircase method using n-butanol as the odorant. Normative data has been established using testing from a variety of international locations (103). This test can be administered to each nostril separately or both at the same time, can be re-used up to 200 times (79) and takes between 25 and 45 minutes to administer (104). It is also available in an adapted version for the Asian population (79).

Other standardized olfactory tests described in the literature include the San Diego Odour Identification test (13), the Scandinavian Odour Identification Test (105), the European Test of Olfactory Capabilities (106) which combines odour discrimination and identification, and the Alcohol Sniff Test, a threshold test (107).

***Retronasal Smell Function***

Smell function is usually measured "orthonasally" or by sniffing through the front of the nose. However, smells are also detected "retronasally" or through the nasopharynx during food consumption. The retronasal detection of odorants contributes the majority of food flavour while eating. The Olfactory Flavour Threshold Test, developed by Duffy et al. (108), uses orange flavouring presented in sweetened gelatine. Imitation rum, orange extracts, vanilla aroma, and lemon aroma in solution are also used to assess retronasal olfaction (109,110). Retronasal odour detection is a dynamic process and mouth movements such as chewing, swallowing, and spitting can increase the perceived intensity of flavourings (109). Measuring this component of odour perception is important in cancer patients because it may relate to food acceptability better than other olfactory tests (110).

**Self-assessment of taste and smell function**

A subjective taste and smell questionnaire can provide information about subjective perception of chemosensory function. Patients have the opportunity to report the nature of changes to the basic tastes and odours, as well as the impact such changes have on food preferences, dietary intake and quality of life. Most complaints of taste dysfunction are actually the result of an alteration in smell function (88). Therefore it is important to combine self-assessment of chemosensory function with clinical tests to determine if patient perception accurately represents chemosensory alterations.

A subjective taste and smell questionnaire is a fast and low-burden tool for identifying taste and smell alterations in the clinical setting. One such taste and smell survey was developed to evaluate chemosensory function in AIDS patients (4) and used recently with advanced cancer patients (46). This tool yields a chemosensory complaint score (CCS) (0-16) on the basis of fourteen questions addressing the nature and severity of changes to the senses of taste and smell. This taste and smell survey is preferred to others found in the literature because it contains specific questions related to taste and smell function to address the nature of chemosensory complaints, patients describe the effect chemosensory changes have had on their quality of life, and at 14 questions it is relatively short. Another advantage of the self-perceived taste and smell survey is that the numerical score can be used to stratify patients into those with mild, moderate, and severe chemosensory complaints. Grouping patients in this way reveals the association between chemosensory function and dietary intake, quality of life, and symptom burden (46).

**Framing Chemosensory Function in the Context of Food Intake, Quality of Life, and Symptom Burden**

In order to appreciate the complex experience of advanced cancer, chemosensory evaluation should be considered in the context of dietary intake, quality of life and symptom burden. Previous research suggests that advanced cancer patients with severe self-perceived chemosensory problems have an approximate caloric deficit of 900-1100 kcal/day compared to patients with only mild chemosensory complaints (46). Further evaluation of the relationship between chemosensory function, assessed using modern clinical sensory testing, symptom burden and caloric intake is needed in order to understand the impact of concurrent pain and symptom profiles on nutritional intake.

***Food Intake***

Both taste and smell contribute to the flavour and palatability of food (2). When taste and smell are altered, food preferences may change and the pleasure of eating is significantly reduced (111). Taste perception has an important role in controlling salivary, gastric, intestinal and pancreatic secretions (87). These cephalic phase responses prime the body for nutrient absorption and utilization (112). When taste and smell are altered the sensory stimulation of appetite, and in turn food intake, may be reduced.

Common methods to evaluate food intake include food recalls, food records, and food frequency questionnaires (113). Food records are the best method to assess nutrient intake because they do not rely on the patient's recollection of past intake (114). However, in situations where time is limited, a 24-hour recall may be the most appropriate method of determining food intake. Evaluation of current food intake using food records reveals the calorie and nutrient content of food taken in.

Food record data can also be evaluated using dietary pattern analysis to describe the type and variety of food eaten by a population (115,116). For dietary pattern analysis, food items are classified into food categories on the basis of similarities and differences in macronutrient composition and culinary role (117). Factor or cluster analysis can then be used to determine dietary patterns. Cluster analysis has been used successfully to identify dietary patterns in many previous studies (116-119). Diet patterns labelled "meat", "milk", "white bread", and "healthy" (high in fruit) have consistently been identified in study populations (116-119). One previous study has established three distinct diet

patterns in advanced cancer patients (117). In this study population, 58% of patients followed a diet defined by meat and potatoes, 26% of patients consumed the majority of energy from fruit and white bread, and 16% of patients had a predominantly liquid diet of soup, milk, and nutritional supplements. Further exploration of dietary patterns in relation to taste and smell function may identify specific patterns of eating associated with the nature and severity of chemosensory changes.

***Quality of Life***

A relationship between chemosensory disorders and QOL has been established in patients with head and neck cancer (30,120), those treated with chemotherapy (51), and those in the advanced stages of disease (46). Many researchers have assessed the impact of chemosensory disorders on quality of life of non-cancer populations. Approximately half of patients seeking treatment at a taste and smell clinic reported that their chemosensory dysfunction had affected their QOL (88). Patients attributed changes in appetite, body weight, daily living, and psychological well-being to their taste or smell disorder. Mattes & Cowart (121) found that patients with chemosensory dysfunction had a decreased appetite, decreased food enjoyment, changes to dietary patterns and food aversions when compared to healthy individuals. Van Toller (122) reported that patients diagnosed with an olfactory disorder felt vulnerable because of food safety, personal safety and bodily hygiene concerns. Food preferences were altered and it was easy for patients to forget about the need to eat. Another major complaint was the lack of understanding and sympathy from health professionals about the problem. Patients rarely received counselling to deal with their chemosensory complaints (122).

The Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire can be used to assess QOL in cancer patients (123). This validated questionnaire measures the primary QOL domains of physical, social/family, emotional, and functional well-being, as well as nutritional QOL. The overall QOL score is calculated by summing the five individual QOL domains; higher scores indicate better QOL.

***Symptom Burden***

Taste changes in cancer patients are known to cluster with other distressing symptoms such as fatigue, weakness, weight loss, poor appetite, nausea, and vomiting (33). Common cancer symptoms are frequently measured using the Edmonton Symptom Assessment System (ESAS) (124). Nine cancer symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing, and shortness of breath) are rated on an 11-point scale (0=no symptom, 10=worst possible symptom), thus higher ESAS scores indicate higher symptom distress.

**Conclusion**

Changes in the taste and smell perception of cancer patients are related to a number of factors including cancer treatments and metabolic deficiencies. Many previous research studies report only the presence or absence of chemosensory symptoms as reported by the patient or the results of isolated clinical tests of a single facet of taste or smell function.

There have been no studies using a multi-dimensional approach combining patient perception with clinical test procedures to understand how taste and smell function is affected in cancer. Examination of both major components of food flavour through the application of modern sensory testing techniques will better explain how chemosensory dysfunction leads to a decreased food intake and weight loss. Updating chemosensory knowledge as it relates to cancer will provide the basis for more effective dietary advice and the development of food products to counteract the sensory inhibition of food intake seen in cancer patients.

A missing link in oncology research as it relates to chemosensory changes is framing the results within the context of the overall cancer experience. The relationship between food intake and chemosensory function has received limited research attention in cancer patients. The loss of food enjoyment that results from chemosensory alterations may compound other detriments to quality of life. Combining chemosensory research results with food intake measures, quality of life assessments and symptom burden information will increase our appreciation of the importance of taste and smell changes for patients. Improving food intake and enjoyment by counteracting taste and smell changes will help to improve the quality of life of patients with advanced cancer.

**Research Objectives**

This research was conducted to increase current knowledge regarding taste and smell dysfunction in advanced cancer patients and to evaluate the importance of chemosensory changes in the context of dietary intake and QOL.

The specific objectives were:

1) To characterize the chemosensory profile of individual advanced cancer patients using a comprehensive set of modern chemosensory evaluation techniques. The results of this objective are described in chapter 2
2) To determine if patients' perception of chemosensory function is reflected in clinical chemosensory test results. The results of this objective are described in chapter 3.
3) To determine if there is a relationship between clinical chemosensory function and food intake, quality of life, and symptom burden assessments. The results of this objective are described in chapter 3
4) To describe the influence of self-perceived chemosensory function and symptom burden profile on dietary pattern and food intake. The results of this objective are described in chapter 4.

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# Chapter Two

## Individual Chemosensory Profiles of Advanced Cancer Patients

### Introduction

Cancer patients are commonly held to experience chemosensory abnormalities, however patients are infrequently asked to describe their taste and smell perception and comprehensive clinical assessments are rarely made. Previous chemosensory research used mainly isolated tests of a single facet of taste and smell function. A comprehensive research approach is valuable to assess patient perception of chemosensory ability as well as clinical taste and smell function. There have been no previous studies using a multi-dimensional approach combining patient perception with clinical test procedures for a complete understanding of how taste and smell function is affected in advanced cancer.

Chemosensory research in oncology patients rarely frames the results within the context of the overall cancer experience. The loss of food enjoyment that is a consequence of chemosensory alterations may compound other detriments to quality of life. Combining chemosensory research results with food intake measures, quality of life assessments, and symptom burden information will increase our appreciation of the importance of taste and smell changes for cancer patients.

Clinical chemosensory testing methods are available to study taste and smell function during cancer progression; however, they have not been applied effectively to oncology research. Prior research using isolated clinical tests of a single facet of taste or smell function has been inconclusive. The variable results of previous taste and smell

investigations with cancer patients highlight the individual experience of chemosensory alterations (1). Individual experience is often presented in the literature as case studies. This approach highlights the unique aspects of a participant's personal experience. By focussing on a single patient we can better describe the effects of cancer and treatments on taste and smell function and draw attention to the impact of chemosensory impairments on quality of life.

The purpose of this research is to characterize the chemosensory profile of individual advanced cancer patients using a comprehensive set of clinical evaluations emanating from sensory science. A secondary objective is to frame chemosensory distortion in the context of other cancer symptoms, dietary intake, and overall quality of life. Case presentations are used to emphasize the individual experience of taste and smell changes in cancer patients.

**Methods**

The Research Ethics Board of the Alberta Cancer Board provided ethical approval. Written informed consent was collected from the participants.

Validated sensory testing procedures were used for taste and smell evaluation. The University of Pennsylvania Smell Identification Test (UPSIT) was used to determine odour identification ability (10). The Sniffin' Sticks butanol odour detection threshold test (11) was used to assess patients' ability to detect odours. Basic taste threshold testing was used to determine whole mouth taste function (12). Sucrose (sweet), sodium chloride

(salt), citric acid (sour), and caffeine (bitter) were used as tastants. Results from the case study participants were compared to age and sex-matched normative data (11,13-15). Subjective taste and smell complaints were measured using a taste and smell survey (16). This validated tool yields a chemosensory complaint score (0-16) based on the responses to 14 questions addressing changes to the chemical senses.

Nutritional intake was assessed using three-day dietary records. Patients' height, weight, and six month weight loss was self reported and verified with the medical chart if possible. Patients' quality of life (QOL) was assessed using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire (17). Common cancer symptoms were measured using the Edmonton Symptom Assessment System (ESAS) (18). Nutritional risk and symptoms related specifically to food intake were recorded using the Patient-Generated Subjective Global Assessment (PG-SGA) (19).

**Case One**

The first case was a 48 year old female with breast cancer that had metastasized to the bones, liver, and lungs (Table 2.1). The patient had undergone radiation and chemotherapy (Table 2.2), but was not receiving treatment at the time of evaluation (June 2006). No previous weight loss was reported. The patient consumed 1508 kcal/day or 25.1 kcal/kg/day and 67.8 g of protein/day or 1.13 g/kg/day. This patient prepared meals herself and usually ate alone.

This patient received a score of 12/16 on the taste and smell survey indicating severe chemosensory complaints. Foods tasted more sweet and salty and odours smelled stronger to the patient. She sometimes had a persistent bitter taste in her mouth and she occasionally smelled phantom odours. The patient attributed taxotere chemotherapy as the source of the taste and smell changes. Although her chemosensory function had improved since completing chemotherapy, it was still bothersome. Compared to before the cancer diagnosis sweet, salty, and bitter tasted stronger and sour tasted the same. Although the total chemosensory complaint score pointed towards severe chemosensory alterations, the patient rated her abnormal senses of taste and smell as mild. She avoided desserts, fruit juice, coffee, and salty snacks. The increased strength of certain odours, such as body odour and perfume, made this patient uncomfortable in some social settings. This patient gave up her pet cat because the smell of the litter box became overwhelming.

Clinical tests revealed a normal ability to identify and detect odours and a normal sensitivity to sweet, salty, and bitter tastes. This patient was less sensitive to sour than the average adult. When compared to normative data, this patient had an average sense of smell.

Patient one had a poor QOL. Her most severe symptoms were tiredness and drowsiness. She also had dyspnea, pain, and a poor feeling of wellbeing. Symptoms affecting her food intake included poor appetite and chemosensory changes.

**Case Two**

Case two was a 76 year old male with lung cancer that had metastasized to the lymph nodes, brain and stomach (Table 2.1). Patient two was treated with radiation and chemotherapy (Table 2.2), but was no longer receiving treatment at the time of evaluation (January 2006). The patient reported a 20% weight loss in the past six months. He consumed 936 kcal/day or 11.9 kcal/kg/day and 52.6 g of protein/day or 0.67 g/kg/day. This patient lived near his family. His daughter prepared his meals, although he often ate alone.

Patient two had a self-assessed chemosensory complaint score of 9/16 on the taste and smell survey. He was more sensitive to tastes, especially sweet and salty. He occasionally had a salty or sweet taste in his mouth which led to nausea. This patient did not notice any medications which interfered with his senses. He reported a perceived increase in all four basic tastes (sweet, salty, sour, and bitter) and his sense of smell since he was diagnosed with cancer. He avoided exposure to perfumes. The air freshener in his daughter's car bothered him although she did not notice it. He rated his taste changes as moderate and he avoided salty and sweet foods.

This patient reported greater sensitivity to odours; however clinical smell tests indicated a severe loss of smell function. He was diagnosed with severe microsmia according to the UPSIT and hyposmia with the Sniffin' Sticks threshold test. This patient had normal taste thresholds for all basic tastes compared to average healthy adults.

Patient Two had a low quality of life. He was suffering from pain, tiredness, nausea, drowsiness, poor appetite, poor feeling of wellbeing and shortness of breath. The symptoms affecting his food intake included poor appetite, nausea, dry mouth, and pain. This patient was at high nutritional risk due to weight loss, poor food intake, poor functional status, and advanced disease.

**Discussion**

Case presentations are used to highlight the individual experience of taste and smell changes in cancer patients. A recent study by Bernhardson et al. (20) concluded that there was "great individual variation in patterns, intensity, and impact of smell and/or taste changes" for patients undergoing chemotherapy. In the current evaluation, both case patients had completed treatment and reported self-perceived severe chemosensory changes attributed to cancer which persisted into the advanced stages of disease.

Poor food intake and malnutrition are common in advanced cancer patients (21). Case patient one had not lost weight in the six months prior to assessment. She survived for 5.1 months after participating in the study and likely had not yet experienced the severe appetite loss and muscle and fat wasting characteristic of cancer anorexia/cachexia. Case patient two had lost 20% of his weight in the past six months and survived only 1.8 months after study participation. Both patients were eating fewer calories and protein than recommended for cancer patients (22). Eating adequate nutrients may be difficult for patients experiencing many symptoms that inhibit dietary intake. Chemosensory dysfunction has been related to poor dietary intake (1) and QOL (1,7-9). In one study,

severe chemosensory complaints led to a 900-1100 kcal deficit in energy intake compared to patients with no complaints (1). The authors found that poor appetite, nausea, and early satiety occurred with chemosensory dysfunction and together contribute to lower food intake.

The case patients reported that symptoms of poor appetite, nausea, dry mouth and chemosensory changes interfered with food intake. The patients also stated high levels of pain, tiredness, drowsiness, shortness of breath and a poor feeling of wellbeing. They reported that severe changes in taste function directly affected QOL by altering food preference and enjoyment. Smell changes contributed to an aversion to everyday odours such as perfumes, body odours, and pet odours. Chemosensory changes are key elements of symptom burden and should be considered in the assessment of cancer symptoms to determine interventions for the prevention or alleviation of malnutrition and poor QOL.

Gustatory threshold assessments revealed normal basic taste thresholds. Both patients reported an increased sensitivity to odours. However, clinical tests showed that the younger patient had average smell function, while the older patient was hyposmic. It has previously been reported that 60% of advanced cancer patients were hypsomic as diagnosed by an odour identification test (23). Despite the diagnosis of hyposmia, the case patient perceived an enhanced smell function compared to before cancer. These results highlight a disconnect between clinical chemosensory test results and the perception of taste and smell as reported by the patient. The physiological reason for this disconnect has yet to be investigated.

A taste and smell survey was used to evaluate patient perception of chemosensory function. This questionnaire can be self-administered by the patient or administered in a face-to-face interview. We suggest that an interview is the best administration method for this questionnaire. An interviewer is able to clarify ambiguous terms such as sour and bitter which are often confused or unfamiliar to participants and can probe for more in depth responses to open-ended questions, such as descriptions of chemosensory changes or effects on quality of life. This survey, through the open ended questions, begins to elucidate the impact of chemosensory alterations on quality of life. The next step for this research is a qualitative study to clarify the impact of taste and smell disorders on daily living for cancer patients at the end of life.

Chemosensory dysfunction is a common symptom of cancer that impacts food preference and enjoyment. Both patients profiled here experienced unique chemosensory complaints resulting in an individual profile of chemosensory distortion. The chemosensory function measured by clinical tests appears to be different than that perceived by the patient. Chemosensory complaints occurred with other symptoms, all of which may play a role in decreasing food intake and QOL. Although taste and smell changes are common and disturbing to patients, they are not always volunteered or recognized by healthcare providers. Patients are commonly asked to rate symptoms such as pain and nausea; we suggest that patient perception of taste and smell is an important assessment lacking in current cancer care. Taken together, the results of these cases suggest that an individualized strategy to support dietary intake will involve an integrated management of pain and symptom burden including specific deficits to taste and smell function.

Table 2.1: Chemosensory profiles of case study patients

| | Case One | Case Two |
|---|---|---|
| **Gender** | Female | Male |
| **Age** | 48 | 76 |
| **Diagnosis** | Breast Cancer | Lung Cancer |
| **Time to Death (months)** | 5.1 | 1.8 |
| **Height (cm)** | 175 | 169 |
| **Weight (kg)** | 60.1 | 78.5 |
| BMI | 19.6 | 27.5 |
| 6 month weight loss (%) | 0 | 19.5 |
| **Food Intake** | | |
| Energy (kcal/day) | 1508 | 936 |
| (kcal/kg/day) | 25.1 | 11.9 |
| Protein (g/day) | 67.8 | 52.6 |
| (g/kg/day) | 1.13 | 0.67 |
| **Taste and Smell Survey** | | |
| Total complaints | Severe | Moderate |
| Sweet tastes | Stronger | Stronger |
| Salt tastes | Stronger | Stronger |
| Sour tastes | As strong | Stronger |
| Bitter tastes | Stronger | Stronger |
| Odours smell | Stronger | Stronger |
| **Taste Thresholds** | | |
| Sweet sensitivity | Normal | Normal |
| Salt sensitivity | Normal | Normal |
| Sour sensitivity | Low | Normal |
| Bitter sensitivity | Normal | Normal |
| **Smell Function** | | |
| Odour identification | Normosmia | Severe Microsmia |
| Odour threshold | Normosmia | Hyposmia |
| **Quality of life** | | |
| FAACT | Below average | Below average |
| **Symptoms Experienced (ESAS /10)** | | |
| Pain | 3 | 6 |
| Tired | 7 | 6 |
| Nausea | 0 | 5 |
| Depression | 0 | 0 |
| Anxiety | 0 | 0 |
| Drowsy | 7 | 4 |
| Appetite | 1 | 7 |
| Feeling of wellbeing | 3 | 6 |
| Shortness of breath | 4 | 6 |
| **Nutritional Symptoms (PGSGA)** | | Nausea |
| | No appetite | No appetite |
| | Smells bother me | Pain |
| | Things taste funny/no taste | Dry mouth |

Table 2.2: Treatment history of case study patients

| | **Case One** | **Case Two** |
|---|---|---|
| Date of study participation | June 28 & 29, 2006 | January 17 & 18, 2006 |
| Chemotherapy | 2 cycles FEC100 (Jan/Feb 04)<br>6 cycles Taxotere (Mar-Jun 04)<br>4 cycles Capecitabin (Feb-May 06) | 4 cycles Vinorelbine (Nov/Dec 05) |
| Radiation | Unknown dose to breast, axilla, sternum (Aug-Oct 04)<br>800 cGy to lateral right ribs in 1 fraction (Mar 06)<br>2000 cGy to left hip and femur in 5 fractions (Mar 06)<br>800 cGy to anterolateral ribs in 1 fraction (Apr 06) | 3000 cGy to chest in 10 fractions (Sept 04)<br>2000 cGy to brain in 5 fractions (July 05) |

FEC100: 5-fluorouracil, epirubicin, cyclophosphamide; cGy: centigray

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# Chapter Three

## Chemosensory Function Revealed: Self-Assessed Taste and Smell Perception Does Not Agree with Clinical Tests of Olfaction and Gustation for Advanced Cancer Patients

### Introduction

The chemical senses of taste and smell contribute to safety and quality of life in humans. Chemosensory disorders pose a danger to health when food intake is substantially inhibited. Taste and smell dysfunction will affect food enjoyment, disrupt the cycle of food preparation and consumption in the family and hence decrease quality of life (QOL). Cancer patients are infrequently asked to describe their taste and smell disorders and clinical assessments are rarely made. Yet when studied, these disorders are reported to be common and distressing symptoms of cancer and its treatments (1-4).

Chemosensory research in oncology patients rarely frames the results within the context of the overall cancer experience. The loss of food enjoyment that is a consequence of chemosensory alterations may compound other detriments to quality of life. Taste changes are known to cluster with other distressing symptoms such as fatigue, weakness, weight loss, poor appetite, nausea, and vomiting (5). A relationship between chemosensory disorders and QOL has been established in patients with head and neck cancer (6,7), those treated with chemotherapy (8), and those in the advanced stages of disease (1). Previous research has demonstrated that cancer patients with severe self-perceived chemosensory problems eat fewer calories compared to those with mild complaints (1). Improving food intake and enjoyment by counteracting taste and smell changes may help to improve the quality of life of patients with cancer.

Much of our current understanding of altered taste and smell perception in cancer is based on studies conducted more than twenty five years ago. Since that time methods for chemosensory testing have improved significantly. Many previous research studies report only the presence or absence of chemosensory symptoms as reported by the patient (4,5,9-12) and self-assessment questionnaires of taste and smell have infrequently been applied. A subjective taste and smell questionnaire can provide more complete information about patient perception of chemosensory function. Patients have the opportunity to report the nature of changes to the basic tastes and odours, as well as the impact such changes have on food preferences, dietary intake and quality of life. Most complaints of taste dysfunction are actually the result of an alteration in smell function (13). Therefore it is important to combine self-assessment of chemosensory function with objective clinical tests to determine if patient perception is accurately represented by clinical chemosensory methods.

Objective clinical chemosensory testing methods are available to study taste and smell function during cancer progression; however, they have not been applied effectively to oncology research. The application of modern chemosensory testing techniques has been limited, especially in advanced cancer patients nearing the end of their life. Prior work used mainly isolated clinical tests of a single facet of taste or smell function, often with inconclusive results. This inconsistency may reflect the variety of cancer populations studied, including different cancer types, stages, and treatment protocols (14,15). In addition, the methods used for threshold testing are outdated and few researchers have used current standard methods of taste and smell testing. Modern clinical chemosensory

testing, including standardized methods for measuring taste thresholds, smell thresholds, and odour identification, has been discussed in chapter one of this thesis (16-18). A comprehensive study design using a combination of standard chemosensory tools is lacking in the area of advanced cancer research.

There have been no previous studies using a multi-dimensional research approach combining patient perception with clinical test procedures for a complete understanding of how taste and smell function is affected in advanced cancer. Combining chemosensory research results with food intake measures, quality of life assessments, and symptom burden information will increase our appreciation of the importance of taste and smell changes for patients. The purpose of this research was to determine if patients' perception of chemosensory function was reflected in objective clinical chemosensory test results. It was hypothesized that patients may have difficulty accurately describing alterations to the taste of foods as it is difficult to distinguish between taste and smell when experiencing food flavour. A secondary objective was to determine if there was a relationship between clinical chemosensory function and food intake, quality of life, and symptom burden assessments. We hypothesized that clinically measured chemosensory dysfunction would be related to a decrease in food intake and quality of life and a high symptom burden. The preliminary study results reported here expand the current knowledge of chemosensory dysfunction in advanced cancer patients by combining self-assessed taste and smell perception with clinical tests of olfaction and gustation.

**Methods**

The Research Ethics Board of the Alberta Cancer Board provided ethical approval. Subjects with advanced cancer (defined as locally recurrent or metastatic) were recruited from a regional home care program and the regional cancer treatment center. All patients were over the age of 18, spoke English, and provided written informed consent. Patients were excluded if they had cancers affecting the oral and nasal cavities or esophagus, had received chemotherapy in the past two weeks, or had received radiation to the head and neck region in the past ten days due to the direct effects of these cancers and treatments on chemosensory function and food consumption.

Each patient completed all questionnaires and testing procedures during two evaluation sessions on consecutive days or separated by one rest day. Two sessions, each between 50 and 90 minutes long, were used to minimize physical and sensory fatigue. If a patient was unable to complete all evaluations in two sessions an additional session was added. Sessions took place in the patient's home or at the regional cancer treatment center.

Validated sensory testing procedures were used for taste and smell evaluation. The University of Pennsylvania Smell Identification Test (UPSIT) (Sensonics Inc, Haddon Heights, NJ) was used to evaluate odour identification ability (16). This test is presented in a four-alternative forced-choice format consisting of four booklets, each containing 10 "scratch and sniff" microencapsulated odorants. Two booklets were completed at each evaluation session. The score out of 40 is compared to gender and age normative data.

The Sniffin' Sticks olfactory threshold test (17) (Burghart Medical Technology, Wedel, Germany) was used to assess the patient's ability to detect the presence of an odour. The odour threshold for n-butanol is determined using a single-staircase triple-alternative forced-choice procedure. Three felt-tip pens were presented in a randomized order, two containing the solvent and the third the odorant. The butanol concentration was increased until a staircase reversal was triggered by correct identification of the odorant pen. The threshold is defined as the mean of the last four out of seven staircase reversals. The butanol threshold score (ranging from 0 to 16) is compared to age and gender normative data.

Basic taste whole mouth detection thresholds were measured using a two-alternative forced-choice ascending method of limits (18) with sweet and salt thresholds tested in the first session and sour and bitter thresholds in the second session. Subjects were presented with a pair of stimuli; the tastant dissolved in filtered water and filtered water only. The position of the taste stimulus was randomized across pairs. Subjects began at the lowest concentration and received increasingly stronger concentrations. The subject was asked to determine which of the two stimuli tasted stronger and to describe the taste quality if possible. Tastants were presented as approximately 15 ml of taste solution in half-filled 30 ml plastic glasses. Subjects were asked to swish the solution throughout the mouth and then expectorate. After tasting each pair, subjects rinsed their mouths with filtered water. The subject's detection threshold was the first in a series of three consecutive correctly identified taste stimuli. The taste solutions were prepared using a dilution factor of two. The concentration ranges for the basic taste stimuli were as follows: sucrose (sweet), 0.59

to 1200 mmol/L; sodium chloride (salt), 0.73 to 1500 mmol/L; citric acid (sour), 9.8 X $10^{-3}$ to 20 mmol/L; caffeine (bitter), 2.0 X $10^{-2}$ to 40 mmol/L. These concentrations were based on those reported by taste and smell clinics (18). Taste threshold results are compared to gender normative values (19). These values are not adjusted for age because no age-related changes in taste sensitivity were observed in the normative group (19).

Retronasal smell function was assessed using intensity ratings of vanilla flavouring (Givaudan Canada Inc, Mississauga, ON) in water. Three concentrations of vanilla flavouring (0.33%, 1.0%, 3.0% (v/v)) and one blank water solution were presented in a random order. Overall flavour intensity was rated on a nine point scale anchored with the terms very weak [1] and very strong [9]. This procedure is similar to that used by Koskinen and Tuorila to compare retronasal odour intensity ratings in the young and the elderly (20).

Subjective chemosensory complaints were measured using a taste and smell survey developed to evaluate chemosensory function in AIDS patients (21) and used recently with advanced cancer patients (1). This tool yields a taste complaint score (TCS) (0-10) on the basis of nine questions addressing changes in the sense of taste, changes in the way foods taste, presence of a bad taste in the mouth, changes in specific basic taste qualities (salt, sweet, sour, and bitter), effect of medications on the sense of taste and rating of the severity of taste abnormalities. Similarly, a smell complaint score (SCS) (0-6) is calculated on the basis of five questions addressing changes in the sense of smell, changes in the way foods smell, effect of medications on the sense of smell, changes in

the strength of odours and rating of the severity of smell abnormalities. One point is added for each reported taste and smell complaint and two points for a rating of "severe" or "incapacitating" on the severity of taste/smell abnormality questions. A total chemosensory complaint score (CCS) (0-16) was calculated.

Nutritional status was assessed using three-day dietary records. A registered dietitian instructed patients on completion of the food record and reviewed the records for accuracy and completeness. The nutrient content of food records was determined using the Canadian Nutrient File Database of the Food Processor SLQ Nutrient Analysis Program™ (Esha Research, Salem, OR). Analysis focused on energy and protein intake expressed as kcal/day or kcal/kg body weight (BW)/day and g/day or g/kg BW/day respectively. Patients' height, weight, and history of weight loss over the previous six months was self reported and verified with the medical chart if possible.

Quality of life (QOL) was assessed using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) questionnaire (22). This validated questionnaire measures the primary QOL domains of physical, social/family, emotional, and functional well-being, as well as nutritional QOL. The overall QOL score is calculated by summing the five individual QOL domains; higher scores indicate better QOL.

Common cancer symptoms were measured using the Edmonton Symptom Assessment System (ESAS) (23). Nine cancer symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing, and shortness of breath) were rated on an 11-point scale

(0=no symptom, 10=worst possible symptom). Higher ESAS scores indicate higher symptom distress. Nutritional risk was assessed using the Patient Generated Subjective Global Assessment (PGSGA) (24). A score is generated based on the patient's report of weight change, food intake, nutritional symptoms and functional capacity. A higher score on the PG-SGA indicates higher nutritional risk.

**Data Analysis**

All statistical analyses were preformed using the Statistical Package for the Social Sciences (SPSS for Windows, version 14, SPSS Inc. Chicago). Descriptive statistics were used to determine the prevalence of chemosensory abnormalities measured using both the taste and smell survey and the clinical chemosensory tests. Basic taste results are reported as geometric means. Concentrations of taste stimuli were transformed to log values for graphic representation of detection thresholds. Pearson correlation analysis was used to assess the relationship between self-perceived chemosensory complaints and clinical test results. Individuals were stratified into three groups based on standard deviation of the chemosensory complaint score. One-way ANOVA (with Tukey test for post hoc analysis) was used to compare energy and protein intakes, age, weight loss, BMI, nutritional risk, quality of life and ESAS symptoms across the three chemosensory complaint groups. Patients were similarly grouped based on standard deviation of clinical chemosensory test results. The Kruskal-Wallis test was used to compare the retronasal flavour intensity ratings based on patients' self-perception of chemosensory ability. The Kaplan-Meier product limit estimate was used for survival analysis (with Mantel-Cox log-rank significance test).

**Results**

Thirty one patients ranging in age from 36 to 88 participated in the study between September 2005 and January 2007. Characteristics of the study population are shown in Table 3.1. One patient did not complete any clinical chemosensory tests and one patient completed only the first evaluation session.

***Clinical Chemosensory Assessments***

Results of the clinical chemosensory tests are shown in Table 3.2.

**Odour Identification (UPSIT) (n=29):** Four patients (14%) had normal odour identification ability while decreased olfactory function was noted in 25 patients (86%). Patients with lower UPSIT scores were significantly older (77.4 ± 7.1) than patients with higher scores (57.7 ± 11.5; p=0.023). Compared to normative data, 24 patients (83%) scored less than the 50$^{th}$ percentile for age and sex and 13 patients (45%) scored less than the 25$^{th}$ percentile.

**Olfactory Detection Threshold (Sniffin' Sticks) (n=30):** Fifteen patients (50%) had normal odour threshold scores and 15 patients (50%) had decreased olfactory thresholds. Fourteen of these patients were hyposmic as diagnosed by both the odour identification and detection tests. Compared to normative data, 19 patients (63%) were below the 50$^{th}$ percentile for age and sex and 15 patients (50%) were below the 25$^{th}$ percentile.

**Basic Taste Threshold (sweet n=30, salt n=30, sour n=29, bitter n=28):** The detection thresholds for the basic tastes are presented in Figure 3.1. These graphs illustrate the range of taste detection thresholds obtained for the group. Twenty-five patients (83%) had normal sweet threshold, 15 patients (50%) had normal salt threshold, six patients

(21%) had normal sour threshold, and 17 patients (61%) had normal bitter threshold. The remaining patients had an increased threshold for the basic tastes.

***Subjective Chemosensory Complaints***

Twenty-nine subjects (93%) reported chemosensory dysfunction for at least one of the 14 questions on the taste and smell survey (Table 3.3). Of these, 22 (71%) had both taste and smell complaints, 6 (19%) had only taste complaints and one subject (3%) had only smell complaints. When comparing chemosensory perception to before the diagnosis of cancer, the most commonly reported alteration was an increased sensitivity to basic tastes and odours. For example a change in taste perception was most often reported for salt with 52% of patients perceiving salt as stronger than before they were diagnosed with cancer and 13% finding salt to be weaker. While the majority of patients reported changes in taste and smell since being diagnosed with cancer, this was not often related to specific medications they were taking. Only 29% of patients felt medications had affected taste function and 13% reported that medications had affected smell function. Patients reported that changes to taste and smell function had negatively impacted their quality of life because of changes in appetite, food preferences and food enjoyment.

***Perceived Chemosensory Function versus Clinical Tests***

There is no significant correlation between the chemosensory complaint score and any of the clinical taste or smell tests (data not shown). There is a moderate linear association between the two clinical smell tests of odour identification and odour detection threshold ($r=0.478$, $p= 0.009$) (Figure 3.2).

A comparison between clinical chemosensory test results and patient perception of chemosensory function for each basic taste and odour function is shown in Table 3.4. The number of participants in each group (patients reporting a perception of "stronger", "as strong", or "weaker" chemosensory perception) is small, particularly for patients reporting a weaker taste sensation. Consequently comparisons of the mean clinical taste and olfactory tests are difficult to interpret. It was felt that useful information could be obtained using a graphic representation of each individual's chemosensory results. The taste detection threshold results were divided as to whether patients reported a stronger taste sensation, the same taste sensation, or a weaker taste sensation (Figure 3.3). It appears that patients reporting an increased sensitivity to the basic tastes ("stronger perception") have similar detection thresholds to those reporting the same taste sensation as before the onset of cancer ("as strong"). There are a few patients reporting that salt (4), sour (1), and bitter (1) taste stronger who do have lower clinical detection thresholds for these tastes. We can see that the two patients reporting weaker sour perception do in fact have high detection thresholds, however many patients reporting the same or stronger sour taste also have similar threshold values. On the other hand two patients reporting that salt tastes weaker actually have low detection thresholds, indicating a stronger sensitivity to salt, similar to several patients reporting that salt tastes stronger.

Odour identification and threshold results were similarly divided as to whether patients reported "stronger", "as strong", or "weaker" smell sensation (Figure 3.4). There was a trend for patients perceiving stronger smell function to have higher odour identification

scores (Table 3.4); however the mean score for patients in this group would result in a diagnosis of hyposmia. Patients reporting that smells are stronger do not appear to have higher odour threshold scores. Two of the patients reporting weaker smell function did in fact have low scores for both odour identification and odour detection threshold.

Results of the retronasal flavour intensity ratings were divided as to whether patients reported "stronger", "as strong", or "weaker" smell perception (Figure 3.5). Patients perceiving their odour perception to be stronger than before cancer did not appear to have stronger intensity ratings for most of the vanilla solutions. Only the 1% vanilla solution was rated significant stronger by patients reporting "stronger" smell perception compared to those reporting "as strong" or "weaker" perception (Table 3.5).

***Chemosensory Function and Clinical Variables***

Patients were grouped by total chemosensory complaint scores into three groups: Insignificant/Mild (0-3), Moderate (4-10), and Severe (11-16). Patients with severe chemosensory complaints ate significantly fewer calories and grams of protein, were at higher risk for malnutrition and had a lower functional capacity compared to those with insignificant/mild complaints (Table 3.6). Patients with severe complaints also had a significantly shorter survival time than those with fewer complaints ($p=0.024$) (Figure 3.6). Patients with severe complaints had significantly lower QOL than those with insignificant/mild complaints (Table 3.7). This was true for physical well-being, functional well-being, and anorexia-cachexia related nutritional QOL. Patients with severe chemosensory complaints had significantly higher ESAS symptom scores than

patients with fewer complaints for all symptoms except pain, anxiety and nausea (Table 3.8). In particular, patients with severe complaints have much worse appetite and feeling of wellbeing ($p<0.001$) than those with insignificant, mild, or moderate taste and smell complaints.

When patients were grouped by clinical chemosensory test results no relationship between clinically measured chemosensory function and food intake, quality of life, or symptom scores were found (data not shown). There was a trend towards lower calorie intake in those patients with the poor olfactory detection thresholds (1421 ± 506 kcal/day) compared to patients with higher thresholds (2040 ± 406 kcal/day; $p=0.058$).

**Discussion**

A comprehensive study design including modern clinical chemosensory testing techniques, a three-day dietary record, and self-assessed chemosensory, symptom, and QOL questionnaires were used to investigate the relationship between taste and smell function, food intake, QOL, and symptom burden in advanced cancer patients. A large percentage of patients (93%) reported some level of altered chemosensory function. In previous studies between 26 and 82% of advanced cancer patients report taste changes (1,9-12) and between ten and 57% report smell changes (1,12). The use of a taste and smell survey with specific questions related to taste and smell function could yield different results than a simple question such as "have you experienced taste or smell changes?" explaining the wide variation in prevalence of chemosensory changes reported in the literature. For example a patient may say no to the question "have you noticed a

change in your sense of taste?", but may report that the perception of one of the basic tastes has changed when probed with more detail. The goal of this research was to comprehensively evaluate patients with altered taste and smell function; therefore we may have recruited a greater proportion of patients experiencing chemosensory changes than in previous studies. Although patients may have been interested in the study if they were experiencing taste and smell alterations, the demographic characteristics are similar to those found in larger study populations (1, Chapter 4), suggesting that the results reported here could be generalized to the broader advanced cancer patient population.

Two tests, each measuring a different component of olfaction, were used to evaluate both dimensions of olfactory processing. The UPSIT measures the ability to identify or label odours and the Sniffin' Sticks measure the detection threshold of butanol. Eighty-six percent of patients had hyposmia (poor smell function) diagnosed by the UPSIT and 50% of patients had hyposmia diagnosed by the Sniffin' Sticks threshold. Nearly all of the patients diagnosed as hyposmic with the odour detection threshold were also hyposmic based on the identification test. However many patients were not able to identify odours when presented at suprathreshold levels despite having an age-normal threshold for butanol.

If the cause of olfactory dysfunction occurred at the level of central odour processing this could explain the inability to identify odours despite normal detection ability. In the only previous study measuring smell function in advanced cancer patients, 60% were hypsomic as diagnosed by an odour identification test (25). This test consisted of a

multiple-choice format similar to the UPSIT, however only seven odours were identified instead of 40. More reliable results are expected from an olfactory test with more odorants (26). We found a greater number of patients with impaired odour identification ability in this study. This could be related to the differences in study population. Yakirevitch et al (25) studied all eligible patients admitted to a hospice unit. For this study we recruited patients from the community, many of whom were approached for a number of other research studies. We suspect that the focus on taste and smell evaluation would attract those patients experiencing chemosensory changes.

A decline in taste function was also common in this study. Up to 79% of patients had higher than normal taste thresholds depending on the basic taste evaluated, with sour the most frequently impaired. Taste loss has been reported in previous studies of head and neck (27, 28) and other cancer patients (29-31). However, many patients in this study reported a perceived increased sensitivity to the basic tastes. A higher sensitivity to bitter has been shown in taste threshold testing of cancer patients (32-35). Despite the perception of greater sensitivity to basic tastes, lower taste detection thresholds were not observed.

Poor taste and smell function diagnosed by the clinical chemosensory tests used in this study could be due to a number of factors. Chemosensory disorders can be classified as transport, sensory, or neural dysfunctions (36). Transport dysfunctions prevent stimulants from interacting with taste or olfactory cells (36). Chemosensory changes in cancer patients have been related to high levels of inflammatory cytokines, which the body

releases in response to a tumour (37). Inflammation may limit the access of stimulants to the taste or olfactory cells resulting in decreased sensitivity to tastes and/or smells (36).

Sensory dysfunctions affect the peripheral taste or smell receptors (36). An example of this type of deficit would be radiation or chemotherapy damage to taste or olfactory cells. Although patients were not receiving treatment at the time of the study, previous chemotherapy may have contributed to chemosensory dysfunction (38). Chemotherapy drugs target rapidly proliferating cells, like those of the olfactory and gustatory systems, leading to damage and loss of perception. Chemosensory dysfunction caused by chemotherapy may recover over time as taste and olfactory cells regenerate, however alterations can persist if regeneration of receptor cells and nerve fibres is incomplete or disturbed (39). Damage to the taste or smell receptors could result in the higher basic taste thresholds and butanol odour thresholds observed in this study. There would be fewer chemosensory receptors responding to a stimulus, resulting in higher threshold levels.

Neural dysfunction can occur because of damage to the peripheral or central nervous system (36). A reduced ability to accurately identify odours would point to a central mechanism, as odour identification requires a higher cognitive demand (40). Whether the taste and smell dysfunction seen in advanced cancer patients is due to transport, sensory, or neural mechanisms or a combination of all three has yet to be determined. The fact that the majority of patients had difficulty identifying odours, could not accurately perceive chemosensory capability, and did not have cancer that would directly affect taste or smell

receptors or any recent chemotherapy would point to a neural mechanism for chemosensory alterations in this study population.

Another factor contributing to poor chemosensory function in advanced cancer patients is age (41). This is particularly true for smell, with over half of those over 65 and three quarters of those over 80 having some smell loss (42). In this study older age was associated with lower UPSIT scores, however there was no association between age and butanol threshold. Comparing the clinical smell results to normative data reveals that the smell loss observed in advanced cancer patients cannot be explained by age alone. Approximately 50% of patients were below the 25$^{th}$ percentile for their age and gender category. Therefore we suggest that cancer or previous cancer treatment has a role in contributing to poor smell function above that seen in normal aging.

A key finding of this study was that patient perception of taste and smell function did not correlate with the clinical chemosensory test results. There are few other studies where subjective perception of chemosensory function has been compared to objective measurements. Two studies have examined the relationship between self-perception and objective measurement of olfaction in healthy volunteers. In both studies subjective perception of smell function was measured using a visual analogue scale anchored with terms such as "no sense of smell" and "normal sense of smell" or "absent olfactory function" and "excellent olfactory function". No correlation between subjective perception of olfactory function and that measured by clinical tests was found in either study (43,44). In this study we used a more specific taste and smell survey to measure

patients' perception which would possibly correlate better with clinical tests. However no relationship was observed, suggesting that the patients' experience and perception of taste and smell changes cannot accurately be measured by clinical taste and smell tests.

Increased sensitivity to basic tastes is a common complaint of advanced cancer patients (1) as confirmed in this study. However of the patients reporting an increased sensitivity to tastes and odours, many had a marked loss of measured chemosensory function. Very few patients (n=2-6) reported that tastes or odours were weaker than before cancer. Those patients reporting weaker chemosensory function did appear to have the poorest clinical test results for sour threshold, bitter threshold, odour threshold and odour identification. For example, two of the patients reporting weaker smell function were diagnosed with anosmia on both the odour threshold and the odour identification test. The third patient who was diagnosed with anosmia on the odour threshold test reported weaker smell function and was diagnosed with moderate hyposmia on the odour identification test. Although this patient was unable to detect the presence of butanol at all, he was able to identify some odours correctly. This patient may be experiencing general hyposmia and specific anosmia to only certain odours. Specific anosmia has been reported in the literature (45). On the other hand, of the 12 patients who reported that odours "smelled stronger than before they were diagnosed with cancer," ten had poor smell function based on at least one of the clinical smell tests. Patients reporting stronger odour perception did not have higher retronasal flavour intensity ratings for three out of four vanilla concentrations. Many patients reporting stronger taste perception had high thresholds (weaker clinical perception) for salt, sour, and bitter tastes.

Other conditions with self-perceived increased chemosensory function include pregnancy, migraines, and multiple chemical sensitivities. Lower odour thresholds have been found in migraine sufferers (46). The cause of this hyperacuity to odours is unknown, but is in line with a hypersensitivity to other stimuli such as light and noise. In the case of multiple chemical sensitivities, clinical olfactory tests reveal similar smell function between patients and controls; however patients perceive odours as more unpleasant (47). As with cancer, the mechanism for this unpleasant or altered perception of odours is unknown. We suspect that the altered perception of tastes and smells resulting in patients reporting an increased chemosensory function despite having poor clinical test results would be the consequence of a disturbance in sensory signal transduction. One theory presented by Berteretche et al (48) is that during the regeneration of taste cells and nerve fibres after chemotherapy the connections are disrupted in some way resulting in an altered coding of tastes.

The perception of chemosensory function is materially different than the olfaction and gustation quantified by clinical tests. The assessments from the clinical taste and smell tests did not correspond with patient's perception of their own taste and smell ability nor did the scores correlate with the chemosensory complaint scores. The clinical sensory testing techniques are designed to measure a loss of chemosensory function such as the decline observed in HIV/AIDS (21), the elderly (41), and Alzheimer's disease (49,50). In the research setting, clinical olfactory tests may help to clarify the physiology behind the loss of taste and smell function observed in cancer patients. However, the common complaint of patients is a perception of altered and/or increased taste and smell function.

Clinical chemosensory tests do not accurately diagnose this type of complaint. A subjective taste and smell questionnaire is a fast and low-burden tool for identifying taste and smell alterations in the clinical setting and is a more reliable indicator of patient perception than clinical tests. The taste and smell survey used in this study was preferred to others found in the literature because it contains specific questions related to taste and smell function to address the nature of chemosensory complaints, patients describe the effect chemosensory changes have had on their quality of life, and at 14 questions it is relatively short. Another advantage of the self-perceived taste and smell survey is that the numerical score can be used to stratify patients into those with mild, moderate, and severe chemosensory complaints. Grouping patients in this way reveals the association between chemosensory function and dietary intake, quality of life, and symptom burden better than clinical chemosensory tests.

No relationship was found between the clinical chemosensory tests and food intake, quality of life, or symptom burden. However, perceived chemosensory complaints were associated with low food intake, poor quality of life, a high symptom burden, and shorter survival. The taste and smell survey was used to group patients into three chemosensory complaint groups (insignificant/mild, moderate, and severe) for analysis. Patients with severe chemosensory complaints ate significantly fewer calories and protein compared to those with insignificant/mild complaints. Similar results were found by Hutton et al, reporting a caloric deficit of 900-1100 calories per day associated with severe chemosensory complaints (1). There was a trend towards greater weight loss in patients with more chemosensory complaints. An association between taste and smell changes

and weight loss has been reported in other studies (1,12,32). Patients with severe chemosensory complaints were at greater nutritional risk as measured by the PG-SGA and had a shorter survival time than those with fewer complaints. These results highlight the impact of chemosensory changes on the risk of anorexia/cachexia and malnutrition in patients with advanced cancer.

Taste and smell changes had a negative impact on QOL. Patients with severe chemosensory complaints had significantly lower QOL scores for physical, functional, nutritional, and overall QOL. Similar results associating taste and smell complaints with QOL were found by Hutton et al. in advanced cancer patients (1) and Wickman et al. in patients receiving chemotherapy (8). Patients commented that changes in chemosensory function affect QOL through changes in appetite, food preferences and enjoyment. Research in non-cancer patients also link changes in appetite, food enjoyment, dietary patterns, and psychological wellbeing to taste and smell disorders (51,52).

Advanced cancer patients with chemosensory complaints are experiencing a combination of severe palliative symptoms. Patients with severe chemosensory complaints had higher symptom scores for tiredness, depression, drowsiness, appetite, feeling of well-being, and shortness of breath. Hutton et al. found that poor appetite, nausea, and early satiety occurred with chemosensory dysfunction and together contribute to low food intake (1). A recent study by Bernhardson et al. (53) found that symptoms such as appetite loss, early satiety, nausea and oral problems are interrelated with chemosensory changes for patients undergoing chemotherapy. Taste changes appear to cluster with symptoms such

as fatigue, weakness, weight loss, poor appetite, nausea, and vomiting in lung cancer patients (5). It is important to study an entire range of symptoms to provide appropriate advice to prevent or alleviate malnutrition and poor QOL in advanced cancer patients.

This is the first study using a multi-dimensional approach to chemosensory research in advanced cancer patients. There were some limitations to this novel study. The first is the small sample size, with only 31 patients consenting to participate in the study. Although the small sample size limits the statistical analysis and significant results described in this paper, many interesting observations are revealed. Differences between patients reporting "stronger", "as strong", or "weaker" chemosensory function were not clear in this study however trends in the data warrant further research. Sample size calculations based on the data showing promising trends are presented in Table 3.9. To show a significant difference in energy intake for patients with different scores on the odour threshold tests at least 72 patients would be needed. To show a significant difference in odour identification (UPSIT) score for patients perceiving altered smell function at least 36 patients would be needed. This study is only the first look into the area of perceived and measured chemosensory function in advanced cancer patients.

The second limitation of the study was patient fatigue. The comprehensive study design was needed to increase our understanding of taste and smell function in advanced cancer patients and considerations were made to limit fatigue by separating testing into two sessions or more if needed. However, certain procedures such as the butanol odour threshold test were unavoidably lengthy and led to fatigue in some patients. The final

limitation was conducting clinical sensory testing in patients' homes. We were unable to control outside odours and other distractions within the home. Nevertheless, testing was done in the home in order to increase the convenience for patients who wanted to participate in the study although they had physical limitations.

This study is the first to combine self-assessment of chemosensory function with a complete evaluation of clinical taste and smell function in advanced cancer patients. The perception of chemosensory function is materially different than the olfaction and gustation quantified by clinical tests. Although many patients report a perception of increased sensitivity to taste and smell, clinical tests reveal an objective loss of function. The underlying basis of the perception of unpleasant taste and odours in patients with hyposmia and hypogeusia remains to be determined.

Table 3.1: Characteristics of the chemosensory study population

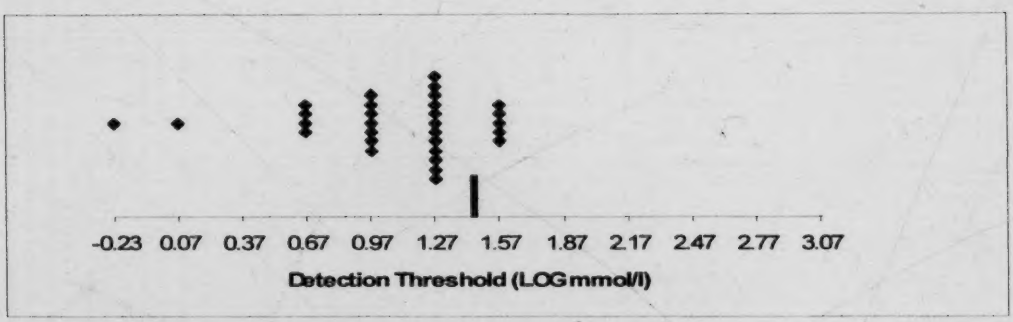
| | **Study Population n=31** |
|---|---|
| Age (years) | 66.1 ± 13.1 |
| Gender (male/female) | 18/13 |
| Median time to death (months) | 8.3 ± 1.8 |
| Previous chemotherapy treatment | 18 (58) |
| Smoking status | |
| Current smoker | 3 (10) |
| Former smoker | 20 (65) |
| Cancer Diagnosis | |
| Lung | 9 (29) |
| Breast | 8 (26) |
| Prostate | 5 (16) |
| Multiple Myeloma | 2 (7) |
| Colorectal | 2 (7) |
| Other | 5 (16) |

Values are mean ± SD or n (%)

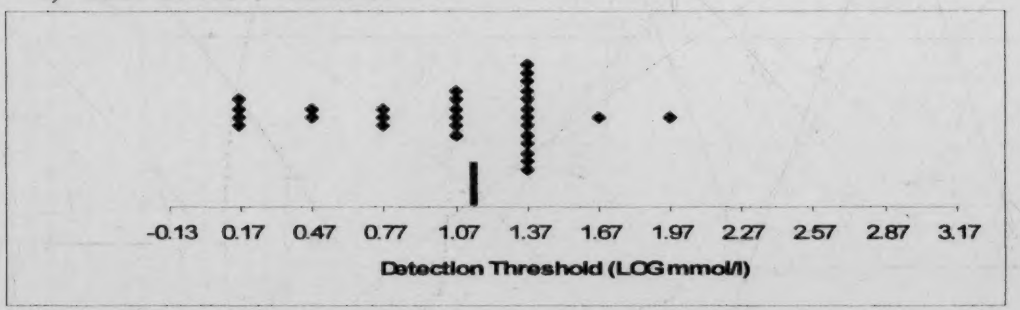
Table 3.2: Clinical chemosensory test results, normative values and diagnoses

| | Study Population Mean | *Normative values (16,17,19)* | Number of patients with Hyposmia/ Hypogeusia n(%) | $< 50^{th}$ percentile n(%) | $< 25^{th}$ percentile n(%) |
|---|---|---|---|---|---|
| Odour identification (UPSIT score x/40) | 28.2 ± 5.9 | *>33* | 25 (86) | 24 (83) | 13 (45) |
| (n) | (29) | | | | |
| Odour detection threshold (x/16) | 5.6 ± 2.7 | *>6* | 15 (50) | 19 (63) | 15 (50) |
| (n) | (30) | | | | |
| Sweet taste detection threshold (mmol/l) | 12.1 | *<25* | 5 (17) | - | - |
| (n) | (30) | | | | |
| Salt taste detection threshold (mmol/l) | 11.5 | *<12 (male) <10* | 15 (50) | - | - |
| (n) | (30) | *(female)* | | | |
| Sour taste detection threshold (mmol/l) | 0.96 | *<0.32 (male)* | 23 (79) | - | - |
| (n) | (29) | *<0.20 (female)* | | | |
| Bitter taste detection threshold (mmol/l) | 1.25 | *<1.5* | 11 (39) | - | - |
| (n) | (28) | | | | |

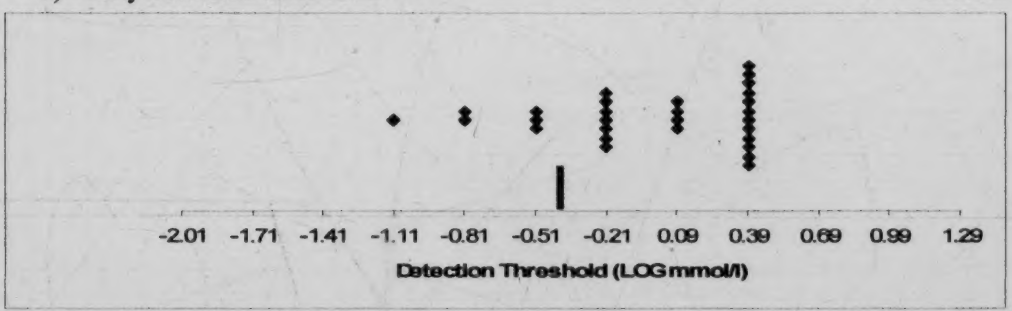
Values are mean ± SD, geometric mean, or n (%)
<50% = number of participants below the $50^{th}$ percentile for age and sex normative data
<25% = number of participants below the $25^{th}$ percentile for age and sex normative data



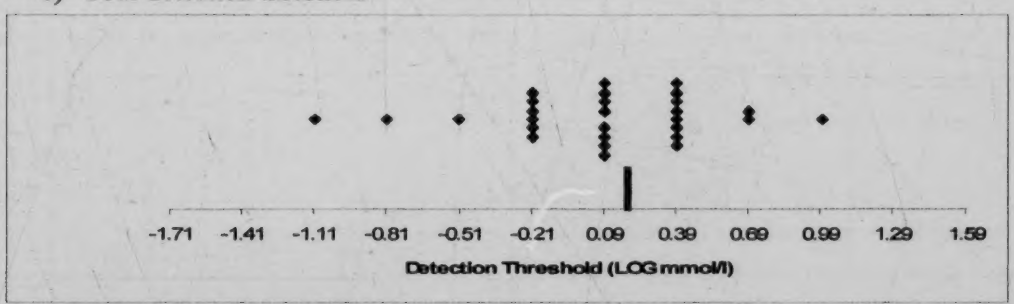

a) Sweet detection thresholds




b) Salty detection thresholds




c) Sour detection threshold




d) Bitter detection thresholds

( ▌= Value above which indicates hypogeusia)

Figure 3.1: Detection thresholds of participants for the four basic tastes

Table 3.3: Frequency of responses to questions on the taste and smell survey

| **Taste Complaint** | **Yes** | **No** |
|---|---|---|
| I have noticed a change in my sense of taste | 21 (68) | 10 (32) |
| A food tastes different than it used to | 20 (65) | 11 (35) |
| I have a persistent bad taste in my mouth | 16 (52) | 15 (48) |
| Drugs interfere with my sense of taste | 9 (29) | 22 (71) |
| Comparing my sense of taste now to before I was diagnosed with cancer… | | |
| Salt tastes: | | |
| Stronger | 16 (52) | |
| As strong | 11 (35) | |
| Weaker | 4 (13) | |
| Sweet tastes: | | |
| Stronger | 12 (39) | |
| As strong | 16 (52) | |
| Weaker | 3 (10) | |
| Sour tastes: | | |
| Stronger | 8 (26) | |
| As strong | 21 (68) | |
| Weaker | 2 (6) | |
| Bitter tastes: | | |
| Stronger | 9 (29) | |
| As strong | 19 (61) | |
| Weaker | 3 (10) | |
| I would rate my abnormal sense of taste as: | | |
| Insignificant | 10 (32) | |
| Mild to moderate | 17 (55) | |
| severe to incapacitating | 4 (13) | |
| **Smell Complaint** | **Yes** | **No** |
| I have noticed a change in my sense of smell | 18 (58) | 13 (42) |
| A food smells different than it used to | 11 (35) | 20 (65) |
| Specific drugs interfere with my sense of smell | 4 (13) | 27 (87) |
| Comparing my sense of smell now to before I was diagnosed with cancer... | | |
| Odours are: | | |
| Stronger | 12 (39) | |
| As strong | 13 (42) | |
| Weaker | 6 (19) | |
| I would rate my abnormal sense of smell as: | | |
| Insignificant | 13 (42) | |
| mild to moderate | 12 (39) | |
| severe to incapacitating | 6 (19) | |

Values are n (%)

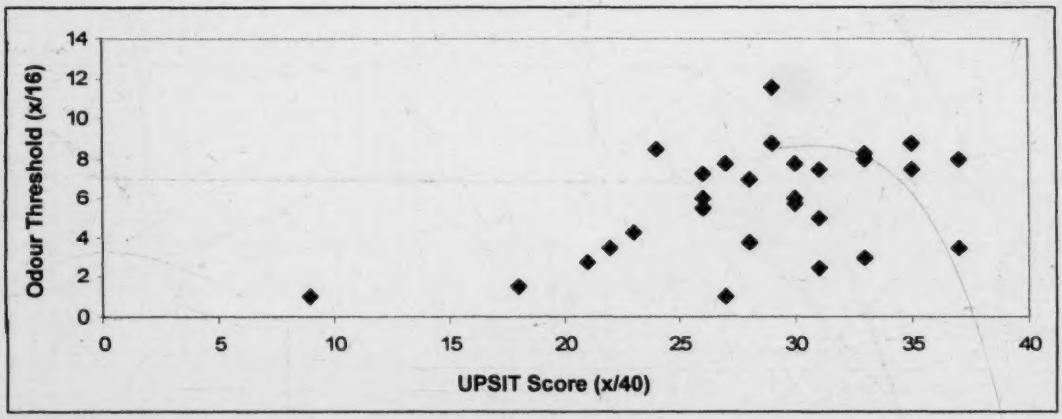
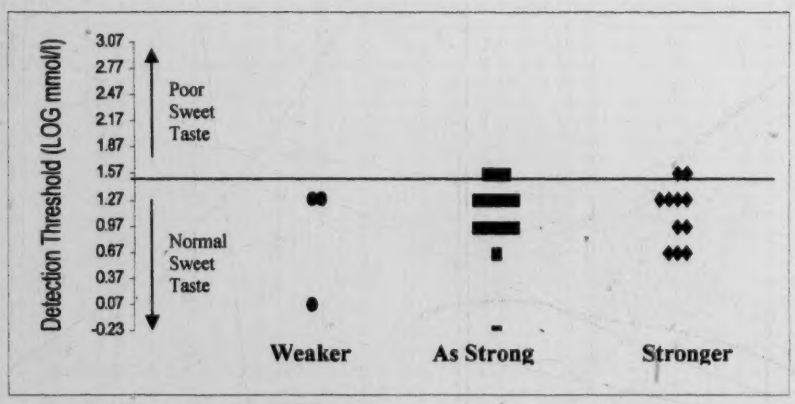



Figure 3.2: Scatterplot of odour identification and odour detection threshold scores

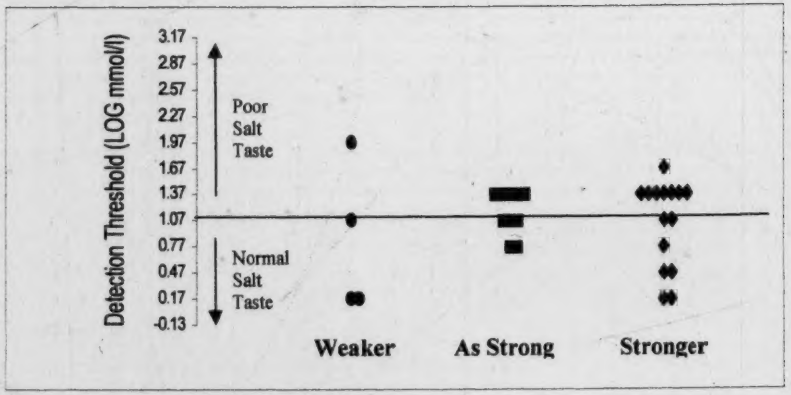
Table 3.4: Objective clinical chemosensory test results compared to self-assessed perception of chemosensory ability reported on the taste and smell survey

| Clinical tests | Self-assessed Chemosensory Perception | | | |
|---|---|---|---|---|
| | Comparing my sense of smell now to before I was diagnosed with cancer odours are … | | | |
| | Stronger | As strong | Weaker | p-value |
| Odour identification (UPSIT score x/40) | 30.9 ± 5.0 | 27.9 ± 3.5 | 24.2 ± 9.3 | .081 |
| (n) | (10) | (13) | (6) | |
| Odour detection threshold (x/16) | 5.5 ± 2.3 | 6.5 ± 2.5 | 4.0 ± 3.2 | .171 |
| (n) | (11) | (13) | (6) | |
| | Comparing my sense of taste now to before I was diagnosed with cancer "basic tastes" are … | | | |
| | Stronger | As strong | Weaker | p-value |
| Sweet taste detection threshold (mmol/l) | 13.3 | 12.4 | 7.4 | - |
| (n) | (12) | (15) | (3) | |
| Salt taste detection threshold (mmol/l) | 11.2 | 14.4 | 7.0 | - |
| (n) | (16) | (10) | (4) | |
| Sour taste detection threshold (mmol/l) | 1.05 | 0.87 | 1.77 | - |
| (n) | (8) | (19) | (2) | |
| Bitter taste detection threshold (mmol/l) | 0.76 | 1.30 | 3.15 | - |
| (n) | (7) | (18) | (3) | |

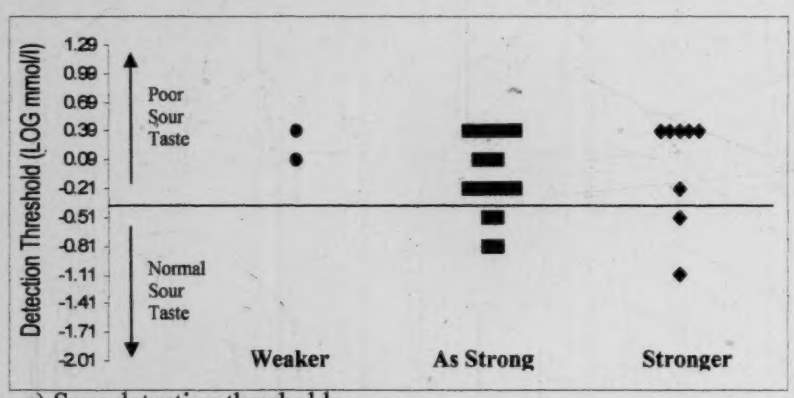
Values are mean ± SD for odours or geometric mean for tastes



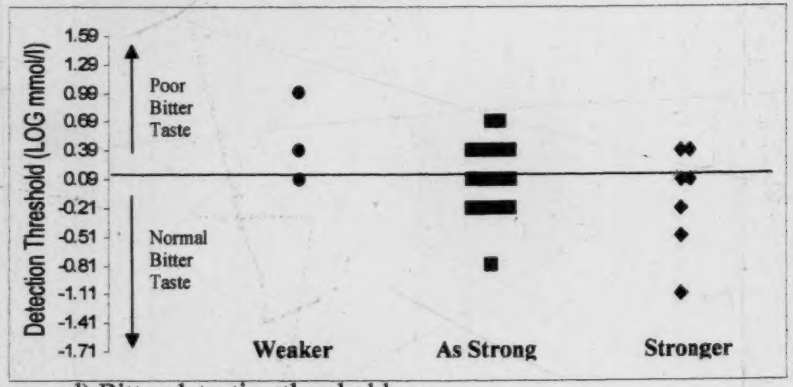

a) Sweet detection thresholds




b) Salt detection thresholds



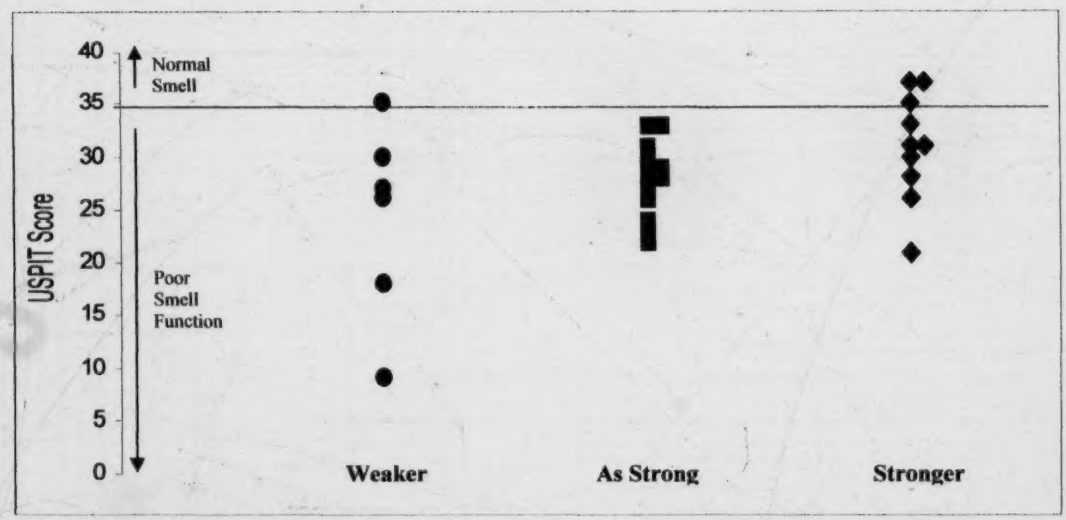

c) Sour detection thresholds



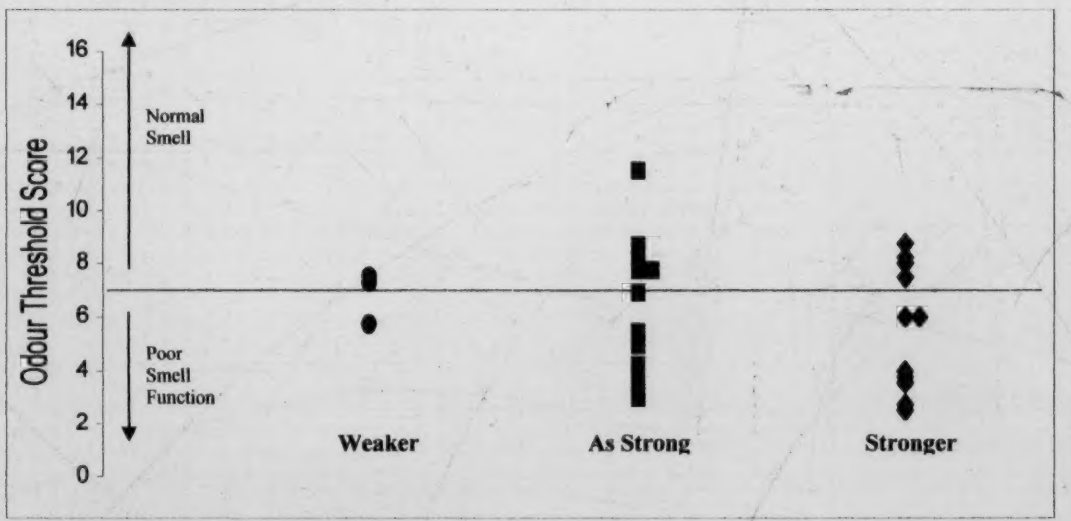

d) Bitter detection thresholds

Note: Lower thresholds indicate a higher sensitivity to the basic tastes

Figure 3.3: Detection thresholds for the basic tastes, (a) sweet, (b) salt, (c) sour (d) bitter, for patients reporting a stronger taste sensation (♦), the same taste sensation (▪), or a weaker taste sensation (•) since the onset of cancer




a) Odour Identification




b) Odour Detection Thresholds

Note: Lower scores indicate a poor smell function

Figure 3.4: Odour identification (a) and odour detection thresholds (b) for patients reporting a stronger smell sensation (◆), the same smell sensation (■), or a weaker smell sensation (●) since the onset of cancer

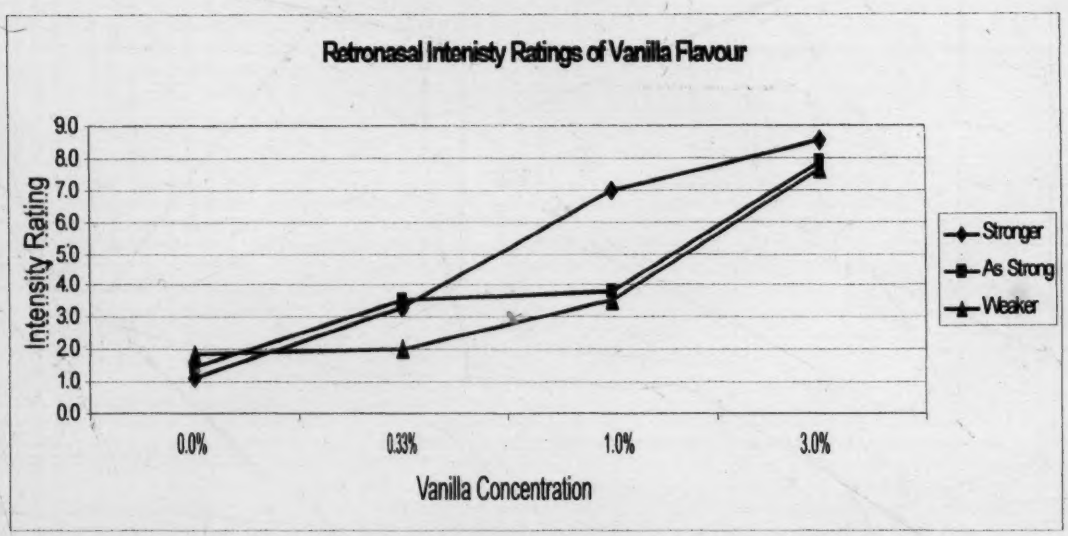



Figure 3.5: Retronasal flavour intensity ratings for vanilla flavouring stratified by self-assessed perception of smell ability reported on the taste and smell survey

Table 3.5: Mean retronasal flavour intensity ratings stratified by self-assessed perception of smell ability reported on the taste and smell survey

| Vanilla Flavouring Concentration | Comparing my sense of smell now to before I was diagnosed with cancer odours are … | | | |
|---|---|---|---|---|
| | Stronger n=7 | As strong n=11 | Weaker n=6 | p-value |
| 0.0% | 1.1±0.4 | 1.5±0.9 | 1.8±1.3 | 0.614 |
| 0.33% | 3.3±2.3 | 3.5±2.1 | 2.0±0.9 | 0.333 |
| 1.0% | $7.0^{a}$±1.4 | $3.8^{b}$±2.1 | $3.5^{b}$±1.2 | 0.005 |
| 3.0% | 8.6±0.5 | 7.9±1.4 | 7.7±1.4 | 0.493 |

Values are mean ± SD

Different superscripted letters within a row are significantly different ($p \leq 0.05$)

Table 3.6: Mean nutrient intake, weight loss, and BMI stratified by self-perceived chemosensory complaint group

| | Insignificant /Mild | Moderate | Severe | p-value |
|---|---|---|---|---|
| Nutrient intake | | | | |
| Kcal/day | $2346^{a} \pm 687$ | $1878^{ab} \pm 678$ | $1362^{b} \pm 756$ | 0.044 |
| Kcal/kg BW/day | $30.8 \pm 10.0$ | $26.2 \pm 10.8$ | $21.4 \pm 14.3$ | 0.327 |
| g/day | $98^{a} \pm 38$ | $75^{ab} \pm 36$ | $46^{b} \pm 28$ | 0.032 |
| g/kg BW/day | $1.3 \pm 0.5$ | $1.0 \pm 0.6$ | $0.7 \pm 0.5$ | 0.168 |
| Age (yr) | $73.3 \pm 7.1$ | $65.2 \pm 13.1$ | $60.9 \pm 15.7$ | 0.193 |
| Nutritional Risk (PGSGA) | $6^{a} \pm 4$ | $12^{ab} \pm 6$ | $19^{b} \pm 8$ | 0.003 |
| Functional Capacity | $1.7^{a} \pm 0.8$ | $2.7^{ab} \pm 1.0$ | $3.1^{b} \pm 1.3$ | 0.045 |
| Weight loss (kg) | $5.2 \pm 10.1$ | $10.5 \pm 7.9$ | $10.0 \pm 8.4$ | 0.381 |
| BMI | $26.0 \pm 3.7$ | $27.9 \pm 5.6$ | $23.4 \pm 3.5$ | 0.131 |

Values are mean ± SD

Different superscripted letters within a row are significantly different ($p \leq 0.05$)

Kcal: kilocalories, BW: body weight, Weight loss: during the previous 6 months, PGSGA: Patient Generated Subjective Global Assessment (Higher scores indicate greater risk for malnutrition); Functional Status (Higher scores indicate lower functional status)

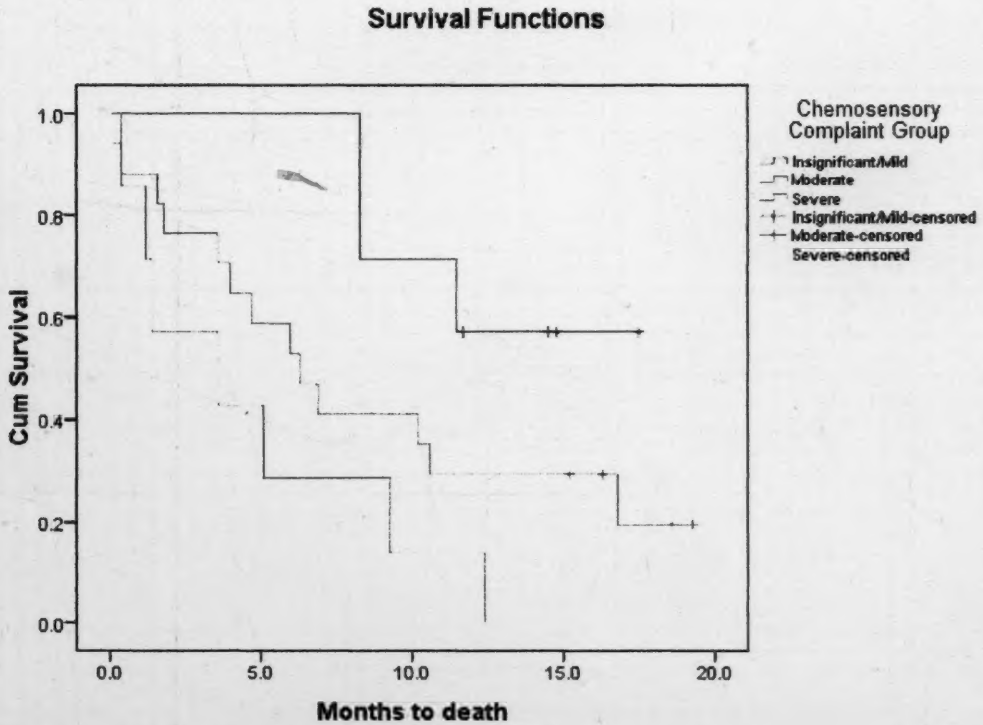



Figure 3.6: Kaplan-Meier survival curves for the three chemosensory complaint groups

Table 3.7: Global and subscale measures of quality of life assessed using the Functional Assessment of Anorexia/Cachexia Therapy (FAACT) instrument stratified by self-perceived chemosensory complaint group

| | Insignificant /Mild | Moderate | Severe | p-value |
|---|---|---|---|---|
| Global QOL (x/156) | $125^{a} \pm 16$ | $107^{ab} \pm 27$ | $78^{b} \pm 26$ | 0.009 |
| Physical well-being (x/28) | $23^{a} \pm 4$ | $17^{ab} \pm 6$ | $11^{b} \pm 7$ | 0.004 |
| Functional well-being (x/28) | $21^{a} \pm 6$ | $17^{ab} \pm 7$ | $11^{b} \pm 6$ | 0.029 |
| Social/family well-being (x/24) | $22 \pm 6$ | $22 \pm 5$ | $21 \pm 6$ | 0.888 |
| Emotional well-being (x/28) | $20 \pm 4$ | $18 \pm 5$ | $13 \pm 6$ | 0.074 |
| Nutritional QOL (x/48) | $38^{a} \pm 5$ | $33^{a} \pm 8$ | $21^{b} \pm 11$ | 0.002 |

Values are mean ± SD
Different superscripted letters within a row are significantly different ($p \leq 0.05$)
QOL: quality of life

Table 3.8: Mean symptom distress score reported on the Edmonton Symptom Assessment System (ESAS) instrument, stratified by self-perceived chemosensory complaint group

| | Insignificant/ Mild | Moderate | Severe | p-value |
|---|---|---|---|---|
| Pain | $2.4 \pm 2.8$ | $2.8 \pm 2.0$ | $5.1 \pm 2.7$ | 0.053 |
| Tired | $1.6^{a} \pm 2.1$ | $4.1^{ab} \pm 2.9$ | $6.3^{b} \pm 1.7$ | 0.007 |
| Nausea | $0.4 \pm 0.8$ | $1.4 \pm 2.1$ | $3.6 \pm 3.9$ | 0.060 |
| Depression | $0.6^{a} \pm 1.1$ | $1.6^{ab} \pm 2.6$ | $4.3^{b} \pm 3.8$ | 0.038 |
| Anxiety | $0.9 \pm 1.6$ | $1.5 \pm 2.7$ | $3.3 \pm 2.7$ | 0.180 |
| Drowsy | $1.0^{a} \pm 1.3$ | $3.1^{ab} \pm 2.8$ | $4.6^{b} \pm 2.4$ | 0.036 |
| Poor Appetite | $1.7^{a} \pm 1.9$ | $4.4^{a} \pm 2.9$ | $7.9^{b} \pm 3.1$ | 0.001 |
| Poor Feeling of well-being | $2.1^{a} \pm 2.1$ | $3.5^{a} \pm 2.2$ | $6.9^{b} \pm 2.3$ | 0.001 |
| Shortness of breath | $0.7^{a} \pm 1.0$ | $2.3^{ab} \pm 2.8$ | $4.9^{b} \pm 3.9$ | 0.034 |

Values are mean ± SD; Scale: 0=no symptom, 10=worst possible symptom
Different superscripted letters within a row are significantly different ($p \leq 0.05$)

Table 3.9: Sample size estimates based on data from the current study

| Stratification | Outcome | Standard deviation of study population | Effect size | Sample Size(n) |
|---|---|---|---|---|
| Odour Threshold Test (3 groups) | Energy intake | 762 | 620 | 24 per group |
| Self-perception of smell function (3 groups) | Smell identification (UPSIT) | 5.9 | 6.7 | 13 per group |

UPSIT: University of Pennsylvania Smell Identification Test

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# Chapter Four

**Chemosensory Alterations and High Symptom Burden are Associated with a Dietary Pattern Defined by Liquid Nutritional Supplements in Advanced Cancer Patients.**

## Introduction

Little is known about the effect of altered chemosensory perception and symptom burden on food intake and preferences in the advanced cancer population, an important consideration when providing nutrition advice to this patient group. Common methods to evaluate food intake include food recalls, food records, and food frequency questionnaires (1). Food records are the best method to assess nutrient intake because they do not rely on the patient's recollection of past intake (2). Evaluation of current intake using food records reveals the calories and nutrient content of food taken in. Food record data can also be evaluated using dietary pattern analysis to describe the type and variety of food eaten by a population (3-5). Dietary pattern research has rarely been used in the cancer population. One previous study has established three distinct diet patterns in advanced cancer patients (6). In this study population, 58% of patients followed a diet defined by meat and potatoes, 26% of patients consumed the majority of energy from fruit and white bread, and 16% of patients had a predominantly liquid diet of milk, soup, and nutritional supplements.

Further exploration of dietary patterns in relation to taste and smell function may identify specific patterns of eating associated with concurrent pain and symptom profiles including the nature and severity of chemosensory changes. The purpose of this study was to describe the influence of self-perceived chemosensory function and symptom

burden profile on dietary pattern and food intake. We hypothesized that patients with self-perceived chemosensory dysfunction and high symptom burden would consume a dietary pattern characterized by a low caloric value, little food variety and a high proportion of liquids similar to the milk and soup pattern described above. The results reported here increase current knowledge of the relationship between pain and symptom profiles and the dietary intake and food choices of advanced cancer patients.

**Methods**

Subjects with advanced cancer (defined as locally recurrent or metastatic) were recruited from a regional cancer treatment center and a home care program. Patients from six studies were pooled for analysis in this paper. Sixty-eight patients had previously been included in a paper on dietary patterns of advanced cancer patients (6). The remaining patients had not been included in this type of analysis before. Written informed consent was collected from participants. All patients were over the age of 18 and spoke English. The study was approved by the Research Ethics Board of the Alberta Cancer Board.

Nutritional status was assessed using three-day dietary records. A research assistant instructed patients on completion of the food record and reviewed the records for accuracy and completeness. The nutrient content of food records was estimated using the Canadian Nutrient File Database of the Food Processor II Nutrient Analysis Program™ (Esha Research, Salem, OR). Analysis focused on energy and protein intake expressed as kcal/day or kcal/kg body weight (BW)/day and g/day or g/kg BW/day respectively as well as protein/energy ratio. For dietary pattern analysis, food items were classified into

one of 20 food categories on the basis of similarities and differences in macronutrient composition and culinary role (6).

Subjective taste and smell complaints were measured using a taste and smell survey developed to evaluate chemosensory function in AIDS patients (7) and used recently with advanced cancer patients (8). This tool yields a taste complaint score (TCS) (0-10) on the basis of nine questions addressing changes in the sense of taste, changes in the way foods taste, presence of a bad taste in the mouth, changes in specific basic taste qualities (salt, sweet, sour, and bitter), effect of medications on the sense of taste and rating of the severity of taste abnormalities. Similarly, a smell complaint score (SCS) (0-6) is calculated on the basis of five questions addressing changes in the sense of smell, changes in the way foods smell, effect of medications on the sense of smell, changes in the strength of odours and rating of the severity of smell abnormalities. One point is added for each reported taste and smell complaint and two points for a rating of "severe" or "incapacitating" on the severity of taste/smell abnormality questions. A total chemosensory complaint score (CCS) (0-16) was calculated.

Common cancer symptoms were measured using the Edmonton Symptom Assessment System (ESAS) (9). Nine cancer symptoms (pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, wellbeing, and shortness of breath) were rated on an 11-point scale (0=no symptom, 10=worst possible symptom). Higher ESAS symptom scores indicate higher symptom distress.

**Data Analysis**

All statistical analyses were preformed using the Statistical Package for the Social Sciences (SPSS for Windows, version 14, SPSS Inc. Chicago). K-means cluster analysis was used to determine dietary patterns following a previously reported procedure (6). Once the 3 dietary patterns were determined, one-way analysis of variance (with Tukey test for post hoc analyses) was used to compare mean energy contribution of each food category, overall energy and protein intake, protein/energy ratio, clinical variables, and symptom scores across the three clusters. Kaplan-Meier produce limit estimate was used for survival analysis (with Mantel-Cox log-rank significance test). Individuals were stratified into four groups based on chemosensory complaint score as in the previous study conducted by Hutton et al (8). One-way analysis of variance (with Tukey test for post hoc analysis) was used to compare energy and protein intake, protein/energy ratio mean energy contribution of food categories, and symptoms scores across the four chemosensory complaint groups. Patients were grouped based on subjective perception of the four basic tastes and odour. One-way analysis of variance was used to compare energy and protein intake and protein/energy ratio in patients who perceived tastes and smells to be "stronger", "as strong", or "weaker" than before cancer diagnosis. Hierarchical multiple regression analysis was used to determine which cancer symptoms contribute to the variation in calorie and protein intakes.

**Results**

Data from 151 patients were collected for this study. Characteristics of the study population are shown in Table 4.1. All patients completed a dietary record and the taste

and smell survey. ESAS symptom scores were recorded for 110 patients. Data was collected a median of 8.6 months before death (range: 0.1 - 42.2 months).

***Dietary Patterns Identified by Cluster Analysis***

The average energy contribution from the 20 food categories are shown in Table 4.2. Three dietary patterns were identified based on the food categories that contributed relatively greater proportions of energy to each cluster.

The first dietary pattern (termed meat/dessert) was characterized by its higher energy contributions from meat and dessert. This pattern also had a higher energy contribution from the "other" food category compared to the fruit/pasta group. The second dietary pattern (termed fruit/pasta) contained a significantly higher intake from fruit and pasta as well as butter, margarine, and added fats. People in the fruit/pasta group also consumed more energy from cheese compared to the liquid/supplement group. The final dietary pattern (termed liquid/supplement) was defined by a higher energy contribution from nutritional supplements such as liquid meal replacement, enteral formula, or protein powder. In the liquid/supplement pattern, patients received 42% of calories from liquids including milk, soup, and nutritional supplements.

***Clinical Variables by Cluster***

Patients in the liquid/supplement group had significantly higher chemosensory complaint scores compared to those in the other dietary patterns (Table 4.3). Patients in the

meat/dessert and fruit/pasta groups had a significantly greater survival time than those in the liquid/supplement group (p=0.002) (Figure 4.1).

Significant differences in mean nutrient intakes were seen across dietary patterns (Table 4.3). Patients in the liquid/supplement pattern had significantly lower daily energy and protein intakes than the meat/dessert group and the fruit/pasta group. However there was no significant difference in energy and protein intake when reported as per kilogram body weight per day or in protein/energy ratios. Supplement users had the lowest weight and BMI compared to the fruit/pasta dietary pattern.

***Symptom Burden by Cluster***

Patients in the liquid/supplement dietary pattern had significantly higher ESAS symptom scores than patients in the other diet patterns except for shortness of breath (Table 4.4). Specifically, high supplement users were in more pain, were more tired and nauseous, and had a worse feeling of wellbeing than patients in the meat/dessert and fruit/pasta groups. Patients in the liquid/supplement group were also more anxious and drowsy and had a worse appetite than patients in the meat/dessert group.

***Chemosensory Complaints***

Patients were grouped by total chemosensory complaint scores into four groups: Insignificant (0-1), Mild (2-4), Moderate (5-9), and Severe (10-16). There was no difference in energy contribution of the 20 food categories between the four chemosensory complaint groups except for the supplement category (data not shown).

Patients in the severe chemosensory complaint group received greater energy from nutritional supplements than patients in the insignificant, mild, or moderate complaint groups ($p<0.001$). The supplement food category contributed 2.5 – 6 times the energy to the diet of the severe chemosensory complaint group than to the other groups. Nutrient intakes by chemosensory complaint group are shown in Table 4.5. Patients with moderate and severe chemosensory complaints ate significantly fewer calories and protein compared to those with insignificant complaints. No significant differences in protein/energy ratios were observed.

A comparison of energy and protein intakes based on patient perception of chemosensory function for each basic taste and odours is shown in Table 4.6. Although not all results reached statistical significance, it appears that patients reporting either stronger or weaker sensitivities to tastes and odours tend to consume fewer calories and protein than patients reporting the same sensitivity as before the onset of cancer. Specifically, patients reporting a weaker sensitivity to salt consumed significantly less protein than patients with the same taste sensation ("as strong") as before the onset of cancer. As well, patients reporting stronger sensitivity to odours ate significantly less calories and protein than patients reporting that odours smelt as strong as before cancer diagnosis. Although the differences between patients reporting stronger, as strong, and weaker sensitivity to sour reached statistical significance, Tukey's post hoc test is unable to reveal which group is statistically different from the others, possibly due to the small number of participants in the group reporting weaker sensitivity. No significant differences in protein/energy ratios

were observed, however there was a trend for patients reporting "as strong" odour perception to have a higher protein/energy ratio.

Patients with severe chemosensory complaints have significantly higher ESAS symptom scores than patients with insignificant complaints (data not shown). Hierarchical multiple regression analysis reveals that 18.3% of the variation in energy intake is explained by chemosensory complaint score and ESAS appetite score (Table 4.7). Chemosensory complaint score was entered into the model first (block 1) and ESAS appetite score was entered into the model next (block 2). Likewise, 21% of the variation in protein intake is explained by chemosensory complaint score and ESAS appetite score (Table 4.8).

**Discussion**

In this study we related dietary patterns of advanced cancer patients to concurrent pain and symptom profiles, with specific attention to chemosensory function. Three dietary patterns were identified. Sixty-five percent of patients followed the meat/dessert eating pattern, 23% were in the fruit/pasta pattern, and 12% ate a large amount of liquids, particularly nutritional supplements. These patterns were similar to those of our prior work reported by Hutton et al (6). In that study, 58% of patients followed a diet defined by meat and potatoes, 26% of patients consumed the majority of energy from fruit and white bread, and 16% of patients had a predominantly liquid diet of milk and soup. These two studies share 68 patients in common. Diet patterns labelled "meat", "milk", "white bread", and "healthy" (high in fruit) have consistently been identified in healthy populations (3-5). Therefore most of the advanced cancer patients in this study are

following similar diet patterns to those seen in the healthy population. However, there is a small but important group of advanced cancer patients consuming a largely liquid diet.

In both this study and that by Hutton et al. (6), the liquid dietary pattern was unique in that 40% of energy intake was derived from liquids including milk, soup, and nutritional supplements. Patients following the liquid/supplement dietary pattern consumed significantly fewer calories and protein and had a lower body mass index than patients in the other dietary patterns. However, there was no difference in protein/energy ratio between the three dietary patterns. A protein/energy ratio of 0.040 is related to a high risk of protein deficiency, suggesting that regardless of which dietary pattern followed advanced cancer patients may be suffering from protein energy malnutrition (10). Patients in the liquid/supplement diet pattern had a high symptom burden and a closer proximity to death (median 3.5 months). The liquid/supplement pattern was associated with a significantly higher burden of pain, tiredness, nausea, anxiety, drowsiness and chemosensory dysfunction compared with the other dietary patterns. This profile of severe symptoms is likely contributing to the poor calorie and protein intake seen in these patients near the end of life. In previous studies poor dietary intake (11,12), problems with eating (13-15) and weight loss (11,13,14,16,17) have been associated with poor survival in cancer patients.

Perceived chemosensory complaints were associated with poor dietary intake. Patients were grouped into four chemosensory complaint groups (insignificant, mild, moderate, and severe) for analysis based on results of the taste and smell survey. Patients with

moderate and severe chemosensory complaints ate significantly fewer calories and protein than patients with insignificant complaints. Similar results were found by Hutton et al, reporting a caloric deficit of 900-1100 calories per day associated with severe chemosensory complaints (8). Patients were then grouped based on their perception of each basic taste and smell as "stronger", "as strong", or "weaker" than before the diagnosis of cancer. Although not always statistically significant, there was a trend toward lower calorie and protein intake in both patients reporting a "stronger" and a "weaker" perception of the chemical senses. Therefore, it appears that chemosensory alterations, regardless of the nature of dysfunction, contribute to changes in the diet to the detriment of nutrient intake. There were few patients reporting "weaker" chemosensory perception, which may explain why differences in calorie intake were not statistically significant despite a discrepancy of up to 400 kcal/day, which would be considered a nutritionally significant difference. As seen in other studies, many of our patients complain of an increased sensitivity to odours and tastes (8) and these alterations resulted in a discrepancy of about 200 kcal/day compared to patients who perceived normal chemosensory function. Similar to the results obtained when comparing dietary patterns, there was no significant difference in protein/energy ratios related to chemosensory complaints; however all of the patients were at risk for protein energy malnutrition (10).

Severe chemosensory complaints have been associated with lower nutritional intakes in previous studies (8,18,19). Chemosensory complaints and poor appetite explained approximately 20% of the variation in energy and protein intake of the advanced cancer patients in this study as measured using hierarchical multiple regression. Cancer patients

often report chemosensory complaints, poor appetite, and early satiety as symptoms that contribute to poor food intake (20,21). Other cancer symptoms such as pain, nausea, depression, anxiety, drowsiness, and shortness of breath were not related to the variation in nutrient intake. The goal of palliative care is to control these key symptoms of cancer in order to improve patients' QOL. The majority of patients in this study population had relatively low scores for these symptoms on the ESAS, indicating that the symptoms were under control and therefore less likely to be impacting food intake. Factors related to the other 80% of variation in energy and protein intake remain to be determined. Nutritional issues not measured in this study that may impact energy and protein intake include early satiety, dry mouth, difficulty chewing or swallowing, gastrointestinal symptoms, functional status and food aversions.

A reliance on liquid nutritional supplements appears to be a result of the high symptom burden associated with the end of life. Nutritional supplements are promoted as an addition to oral food consumption in order to increase overall dietary intake. In previous studies, nutritional supplements containing n-3 fatty acids or fish oil were successful in increasing caloric intake and weight in patients with cancer cachexia (22,23). However, results from this study suggest that nutritional supplement use at the end of life does not result in an intake of calories or protein that meets recommendations for cancer patients (24). Similar results were found in a study of frail elderly patients where nutritional supplementation did not result in increased dietary intake and instead replaced habitual food intake (25). In a preliminary study, Martin et al found three responses to oral supplementation in advanced cancer patients (26). Some patients (28%) reduced meal

intake totally compensating for the supplement's energy content, other patients (28%) partially compensated for the supplement by decreasing meal intake, and others (44%) did not change their meal intake resulting in increased total energy intake with supplement use. Therefore, promoting nutritional supplements in advanced cancer patients may not result in the intended increase in nutritional intake for all users and may instead replace usual food intake at the expense of social and quality of life aspects such as food enjoyment and family meal consumption.

High users of nutritional supplements in this study are patients with severe chemosensory complaints. These patients often complain of an increased sensitivity to odours and tastes (8). Previous studies on taste acceptance of nutritional supplements have found little or no significant differences in ratings between cancer patients and controls (27-30). Flavoured supplements are preferred over plain or vanilla supplements (27,29) and milk-based supplements are preferred over other types (28,30). DeWys and Herbst (28) found that patients with a greater sensitivity to bitter tastes were more likely to give supplements a poor taste rating. Most of these studies were conducted over 20 years ago and popular dietary supplement brands and formulations have changed. Martin et al. recently developed a custard nutritional supplement, testing flavour, smell, mouth-feel, and volume, to ensure a palatable product that would appeal to advanced cancer patients (26). This careful attention to the target patient population resulted in high compliance (94%) to the prescribed intake in a pilot study of the supplement's effectiveness (26). This study was of short duration (eight days). Although longer compliance data is lacking, the results of this study suggest that nutritional supplements will be more

acceptable and effective when formulated to meet patient preferences. It is essential to consider the unique taste perception of advanced cancer patients during product development as patients with chemosensory disorders are key consumers of nutritional supplements.

A large proportion of advanced cancer patients (88%) followed dietary patterns based on normal foods such as meats, desserts, and fruit. However, a small but important group of patients (12%) consume a largely liquid diet based on nutritional supplements. These patients have lower nutrient intakes, higher symptom distress, and are closer to death than patients in the other dietary patterns. Patients belonging to the liquid/supplement dietary pattern are characterized by greater chemosensory alterations. Taste and smell changes together with high symptom burden contribute to the poor dietary intake and reliance on liquid nutrition in this group of advanced cancer patients. Although nutritional supplements are used to increase nutrient intake in cancer patients, their use may not result in adequate caloric intake and may instead replace usual food intake. More research is needed to determine the appropriateness of recommending commercial nutritional supplements in terms of palatability and effectiveness in end of life care.

Table 4.1: Characteristics of the chemosensory study population

| | **Study Population n=151** |
|---|---|
| Age (years) | 64.5 ± 12.2 |
| Gender (male/female) | 78/73 |
| Median time to death (months) | 8.6 ± 1.1 |
| Weight (kg) | 72.2 ± 18.0 |
| BMI ($kg/m^2$) | 25.2 ± 5.8 |
| Chemosensory Complaint Score | 5.2 ± 4.1 |
| Cancer Diagnosis | |
| Lung | 36 (24) |
| Colorectal | 33 (22) |
| Breast | 30 (20) |
| Prostate | 14 (9) |
| Gastrointestinal | 11 (7) |
| Other | 27 (18) |

Values are mean ± SD or n (%)
Kg: kilogram; BMI: body mass index; $m^2$: meters squared

Table 4.2: Percentage energy contributions (%kcal/d) from food categories for the total study population and in the three dietary patterns

| Food Category | Population Totals (n=151) | Meat/ Dessert (n=98) | Fruit/ Pasta (n=35) | Liquid/ Supplement (n=18) | P-value |
|---|---|---|---|---|---|
| Butter, margarine fats | 3.7 ± 3.8 | 3.4 ± 3.7[a] | 5.7 ± 4.1[b] | 1.8 ± 1.9[a] | <0.001 |
| Beans | 0.9 ± 2.6 | 0.9 ± 2.4 | 1.1 ± 3.5 | 0.6 ± 1.6 | 0.800 |
| Cereals | 5.7 ± 5.2 | 6.0 ± 5.2 | 4.8 ± 4.8 | 5.7 ± 6.4 | 0.492 |
| Cheese | 2.5 ± 3.3 | 2.5 ± 3.3[ab] | 3.4 ± 3.5[a] | 1.0 ± 2.0[b] | 0.038 |
| Dark bread | 4.0 ± 4.6 | 4.2 ± 4.8 | 4.3 ± 4.3 | 2.0 ± 3.1 | 0.132 |
| Desserts | 9.0 ± 8.2 | 11.5 ± 8.0[a] | 4.1 ± 4.8[b] | 5.0 ± 8.5[b] | <0.001 |
| Egg | 2.4 ± 3.4 | 2.3 ± 3.3 | 2.8 ± 4.2 | 2.2 ± 2.5 | 0.727 |
| Fruit | 8.5 ± 7.2 | 6.3 ± 4.1[a] | 15.9 ± 9.5[b] | 5.7 ± 5.8[a] | <0.001 |
| Ice cream | 2.4 ± 3.9 | 2.5 ± 3.9 | 2.0 ± 3.7 | 2.7 ± 4.4 | 0.774 |
| Milk | 7.8 ± 7.0 | 7.7 ± 6.1 | 8.1 ± 7.2 | 8.2 ± 11.1 | 0.939 |
| Nut | 1.9 ± 3.7 | 1.8 ± 3.6 | 2.9 ± 4.6 | 0.5 ± 0.9 | 0.077 |
| Pasta | 4.6 ± 5.6 | 3.7 ± 4.9[a] | 7.6 ± 6.4[b] | 3.8 ± 5.7[a] | 0.001 |
| Potato | 4.2 ± 4.4 | 4.9 ± 4.7 | 3.2 ± 4.0 | 2.9 ± 3.2 | 0.057 |
| Meat | 14.0 ± 8.4 | 16.2 ± 8.7[a] | 11.0 ± 5.9[b] | 8.2 ± 6.2[b] | <0.001 |
| Salty snack | 1.2 ± 2.6 | 1.4 ± 2.8 | 1.1 ± 2.6 | 0.0 ± 0.0 | 0.098 |
| Soups | 3.2 ± 4.7 | 2.9 ± 4.4 | 2.9 ± 3.7 | 5.2 ± 7.4 | 0.142 |
| Supplement | 4.5 ± 10.2 | 1.4 ± 3.1[a] | 0.5 ± 2.1[a] | 29.0 ± 11.4[b] | <0.001 |
| Vegetable | 3.2 ± 3.3 | 3.1 ± 3.1 | 4.0 ± 3.7 | 2.3 ± 3.3 | 0.153 |
| White bread | 6.4 ± 6.4 | 6.4 ± 5.4 | 7.3 ± 8.9 | 4.4 ± 5.7 | 0.293 |
| Other | 8.9 ± 7.4 | 10.2 ± 7.4[a] | 5.5 ± 6.1[b] | 8.5 ± 7.7[ab] | 0.005 |
| *Liquid** | *15.5 ± 13.3* | *12.0 ± 8.5[a]* | *11.5 ± 8.2[a]* | *42.2 ± 12.1[b]* | *<0.001* |

Values are mean ± SD

Different superscripted letters within a row are significantly different ($p \leq 0.05$)

kcal/d: kilocalories per day

* Liquid includes the milk, soup, and supplement food categories combined

Table 4.3: Clinical variables and nutrient intake in the three dietary patterns

| Clinical variable | Meat/ Dessert (n=98) | Fruit/ Pasta (n=35) | Liquid/ Supplement (n=18) | P-value |
|---|---|---|---|---|
| Age | 65.5 ± 12.5 | 62.9 ± 11.9 | 62.0 ± 11.1 | 0.390 |
| Median Suvival | 10.6 ± 1.5 | 8.9 ± 5.6 | 3.5 ± 0.6 | 0.002 |
| Chemosensory Complaint Score | 4.5 ± 3.9[a] | 4.9 ± 3.8[a] | 9.4 ± 3.4[b] | <0.001 |
| Energy intake | | | | |
| Kcal/day | 1995 ± 776[a] | 1954 ± 650[a] | 1389 ± 752[b] | 0.007 |
| Kcal/kg BW/day | 28.8 ± 11.8 | 26.1 ± 8.8 | 23.1 ± 12.7 | 0.113 |
| Protein intake | | | | |
| g/day | 78.2 ± 33.5[a] | 76.9 ± 28.3[a] | 53.1 ± 35.8[b] | 0.012 |
| g/kg BW/day | 1.1 ± 0.5 | 1.0 ± 0.4 | 0.9 ± 0.7 | 0.209 |
| Protein/energy ratio | 0.040 ± 0.009 | 0.040 ± 0.009 | 0.038 ± 0.012 | 0.769 |
| Weight | 72.3 ± 17.8[ab] | 77.3 ± 19.3[a] | 61.7 ± 12.4[b] | 0.011 |
| BMI | 24.8 ± 5.3[a] | 28.2 ± 6.7[b] | 21.5 ± 3.7[a] | <0.001 |

Values are mean ± SD

Different superscripted letters within a row are significantly different ($p \leq 0.05$)

Kcal: kilocalories; kg: kilogram; BW: body weight; g: gram; BMI: body mass index

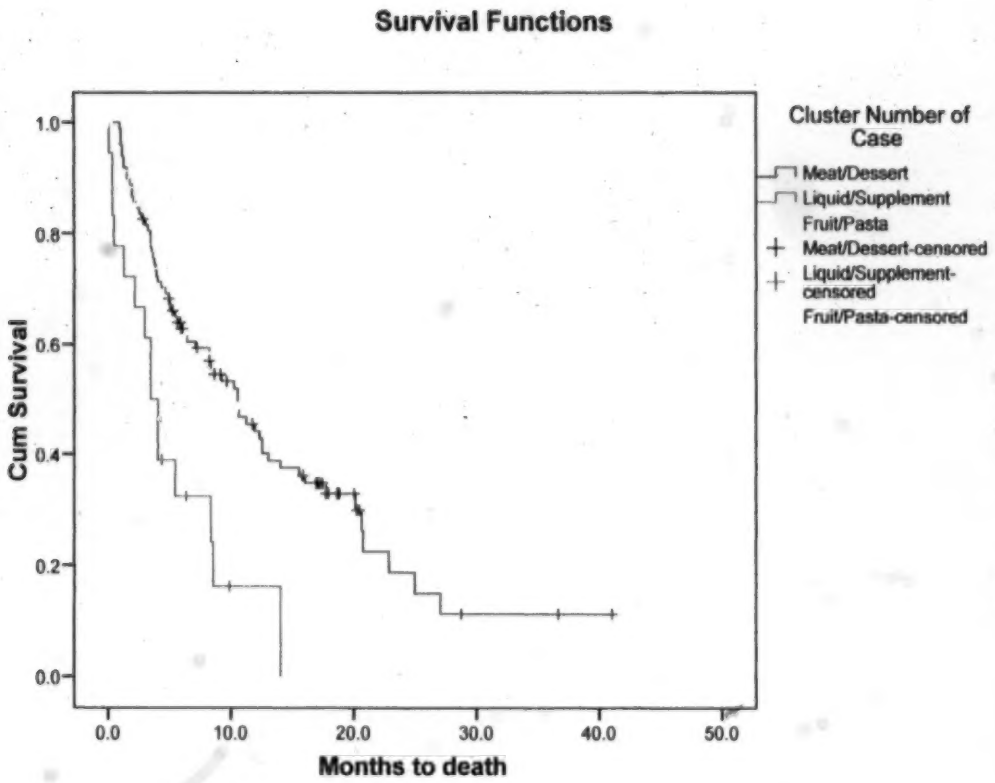


Figure 4.1: Kaplan-Meier survival curves for the three dietary patterns

Table 4.4: Mean symptom distress scores reported on the Edmonton Symptom Assessment System (ESAS) instrument in the three dietary patterns

| Symptoms | Meat/ Dessert (n=77) | Fruit/ Pasta (n=22) | Liquid/ Supplement (n=11) | P-value |
|---|---|---|---|---|
| Pain | $1.7 \pm 2.1^{a}$ | $2.2 \pm 2.3^{a}$ | $5.1 \pm 2.7^{b}$ | <0.001 |
| Tired | $3.3 \pm 2.5^{a}$ | $4.0 \pm 2.3^{a}$ | $6.2 \pm 2.2^{b}$ | 0.001 |
| Nausea | $0.6 \pm 1.3^{a}$ | $1.3 \pm 2.5^{a}$ | $3.7 \pm 3.9^{b}$ | <0.001 |
| Depression | $1.6 \pm 2.3$ | $1.3 \pm 1.7$ | $3.1 \pm 2.5$ | 0.096 |
| Anxiety | $1.5 \pm 2.2^{a}$ | $1.4 \pm 2.1^{ab}$ | $3.2 \pm 2.5^{b}$ | 0.050 |
| Drowsy | $1.8 \pm 2.3^{a}$ | $2.3 \pm 2.2^{ab}$ | $4.3 \pm 3.3^{b}$ | 0.008 |
| Poor Appetite | $2.9 \pm 3.1^{a}$ | $3.7 \pm 2.8^{ab}$ | $5.6 \pm 3.5^{b}$ | 0.020 |
| Poor Feeling of well-being | $3.0 \pm 2.6^{a}$ | $2.9 \pm 1.9^{a}$ | $5.4 \pm 2.7^{b}$ | 0.010 |
| Shortness of breath | $1.7 \pm 2.2$ | $2.0 \pm 2.7$ | $2.8 \pm 3.1$ | 0.304 |

Values are mean ± SD

Different superscripted letters within a row are significantly different ($p \leq 0.05$)

Table 4.5: Mean nutrient intake stratified by self-perceived chemosensory complaint group

| Nutritional Indices | Chemosensory Complaint Group | | | | P-value |
|---|---|---|---|---|---|
| | Insignificant (n=41) | Mild (n=36) | Moderate (n=47) | Severe (n=27) | |
| Energy intake | | | | | |
| Kcal/day | $2291 \pm 616^{a}$ | $1916 \pm 726^{ab}$ | $1834 \pm 824^{b}$ | $1475 \pm 677^{b}$ | <0.001 |
| Kcal/kg BW/day | $31.1 \pm 9.3^{a}$ | $27.8 \pm 11.4^{ab}$ | $26.5 \pm 12.3^{ab}$ | $23.3 \pm 11.7^{b}$ | 0.042 |
| Protein intake | | | | | |
| g/day | $90.9 \pm 30.9^{a}$ | $78.0 \pm 32.3^{ab}$ | $70.7 \pm 33.9^{b}$ | $53.8 \pm 25.2^{b}$ | <0.001 |
| g/kg BW/day | $1.2 \pm 0.3^{a}$ | $1.1 \pm 0.5^{ab}$ | $1.0 \pm 0.6^{ab}$ | $0.8 \pm 0.4^{b}$ | 0.023 |
| Protein/energy ratio | $0.040 \pm 0.010$ | $0.042 \pm 0.010$ | $0.039 \pm 0.009$ | $0.037 \pm 0.008$ | 0.309 |

Values are mean ± SD

Different superscripted letters within a row are significantly different ($p \leq 0.05$)

Kcal: kilocalories; kg: kilogram; BW: body weight; g: gram;

Table 4.6: Nutrient intake stratified based on self-assessed perception of chemosensory ability reported on the taste and smell survey

| | | Subjective Chemosensory Perception | | | |
|---|---|---|---|---|---|
| | Nutritional Indices | Stronger | As strong | Weaker | P-value |
| Salt Perception | Energy (kcal/day) | 1902 ± 848 | 2023 ± 744 | 1605 ± 588 | 0.060 |
| | Protein (g/day) | 71.6 ± 34.9[ab] | 80.8 ± 33.9[a] | 62.7 ± 23.8[b] | 0.044 |
| | Protein/energy ratio | 0.039 ± 0.010 | 0.040 ± 0.009 | 0.040 ± 0.010 | 0.679 |
| (n) | | (44) | (82) | (24) | |
| Sweet Perception | Energy (kcal/day) | 1828 ± 954 | 2014 ± 762 | 1553 ± 176 | 0.064 |
| | Protein (g/day) | 68.2 ± 954 | 80.0 ± 32.4 | 62.1 ± 26.3 | 0.050 |
| | Protein/energy ratio | 0.038 ± 0.009 | 0.040 ± 0.009 | 0.041 ± 0.010 | 0.669 |
| (n) | | (38) | (97) | (15) | |
| Sour Perception | Energy (kcal/day) | 1662 ± 758 | 2014 ± 762 | 1498 ± 325 | 0.028 |
| | Protein (g/day) | 66.3 ± 33.4 | 78.9 ± 33.3 | 51.5 ± 13.7 | 0.035 |
| | Protein/energy ratio | 0.041 ± 0.011 | 0.040 ± 0.009 | 0.034 ± 0.004 | 0.302 |
| (n) | | (31) | (113) | (6) | |
| Bitter Perception | Energy (kcal/day) | 1743 ± 770 | 1991 ± 760 | 1583 ± 676 | 0.137 |
| | Protein (g/day) | 68.1 ± 31.5 | 78.1 ± 33.9 | 61.5 ± 27.1 | 0.181 |
| | Protein/energy ratio | 0.040 ± 0.009 | 0.040 ± 0.010 | 0.039 ± 0.008 | 0.993 |
| (n) | | (31) | (112) | (7) | |
| Odour Perception | Energy (kcal/day) | 1696 ± 832[a] | 2067 ± 688[b] | 1723 ± 822[ab] | 0.015 |
| | Protein (g/day) | 60.8 ± 27.6[a] | 84.1 ± 33.8[b] | 66.1 ± 31.6[ab] | 0.000 |
| | Protein/energy ratio | 0.037 ± 0.009 | 0.041 ± 0.010 | 0.039 ± 0.006 | 0.083 |
| (n) | | (44) | (87) | (20) | |

Values are mean ± SD

Different superscripted letters within a row are significantly different ($p \leq 0.05$)

Kcal: kilocalories; g: gram

Table 4.7: Heirarchical multiple regression analysis for caloric intake (kcal/day)

| Symptom | p-value | R-square | Unstandardized (B) coefficient (SE) | Standardized (Beta) coefficient |
|---|---|---|---|---|
| Block 1 | | .100 | | |
| Chemosensory Complaint Score | 0.001 | | -61.67 (17.80) | -.316 |
| Block 2 | | .183 | | |
| Chemosensory Complaint Score | 0.052 | | -36.70 (18.65) | -.188 |
| ESAS Appetite | 0.001 | | -76.36 (23.15) | -.315 |

Kcal: kilocalories; SE: Standard Error; ESAS: Edmonton Symptom Assessment System

Table 4.8: Heirarchical multiple regression analysis for protein intake (g/day)

| Symptom | p-value | R-square | Unstandardized (B) coefficient (SE) | Standardized (Beta) coefficient |
|---|---|---|---|---|
| Block 1 | | .139 | | |
| Chemosensory Complaint Score | .000 | | -3.22 (0.77) | -.373 |
| Block 2 | | .209 | | |
| Chemosensory Complaint Score | .008 | | -2.20 (0.81) | -.256 |
| ESAS Appetite | .003 | | -3.09 (1.01) | -.289 |

g: gram; SE: Standard Error; ESAS: Edmonton Symptom Assessment System

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# Chapter Five

## Summary and Conclusions

Cancer patients are commonly held to experience chemosensory abnormalities; however patients are infrequently asked to describe their taste and smell disorders and clinical assessments are rarely made. Yet when studied, these disorders are reported to be common and distressing symptoms of cancer and its treatments (1-4). Prior chemosensory research used mainly isolated clinical tests of a single facet of taste or smell function. This one-dimensional approach does not necessarily capture the individual experience of taste and smell alterations or frame them in the context of the overall cancer experience. A comprehensive study design using a combination of standard chemosensory tools is lacking in the area of advanced cancer research. Combining chemosensory research results with food intake measures, quality of life (QOL) assessments and symptom burden information will increase our appreciation of the importance of taste and smell changes for cancer patients.

The research for this thesis was conducted to expand the current knowledge of chemosensory dysfunction in advanced cancer patients and to evaluate the importance of chemosensory changes in the context of the overall cancer experience. Our specific aims were: 1) to characterize the chemosensory profile of individual advanced cancer patients using a comprehensive set of modern chemosensory evaluation techniques, 2) to determine if patients' perception of chemosensory function is reflected in clinical chemosensory test results, 3) to determine if there is a relationship between clinical chemosensory function and food intake, QOL, and symptom burden, and 4) to describe

the influence of self-perceived chemosensory function and symptom burden profile on dietary pattern and food intake.

**Are Chemosensory Evaluations Useful in Cancer Research and Oncology Care?**

This study is the first to combine self-assessment of taste and smell function with a comprehensive set of clinical chemosensory test procedures. Patient perception of altered chemosensory function was widespread (93%). Clinical tests of chemosensation showed decreased taste or smell function (i.e. hyposmia or hypogeusia) in up to 86% of subjects. However, in spite of this generalized loss of taste and smell ability, many patients perceived an increased sensitivity to odours and tastes which they found unpleasant.

A key finding of this research is that patient perception of taste and smell function did not correlate with clinical chemosensory test results, suggesting that patients' experience of taste and smell changes cannot be accurately measured using clinical tests. We hypothesized that clinically measured chemosensory dysfunction would be related to a decrease in food intake and QOL and a high symptom burden. However, no relationship was found between the clinical chemosensory tests and these outcomes. It appears that assessing patient perception of chemosensory function provides a better prediction of these clinical outcomes. High chemosensory complaint scores were associated with low food intake, poor QOL scores, and high symptom burden. Patients reported that severe changes in taste function directly affect QOL by altering food preference and enjoyment. We conclude that the taste and smell survey is a fast and low-burden tool that can identify clinically significant taste and smell alterations in advanced cancer patients.

The clinical chemosensory tests are designed to measure a loss of chemosensory function such as the decline observed in HIV/AIDS (5), the elderly (6), and Alzheimer's disease (7,8). However, the common complaint of advanced cancer patients is a perception of altered and/or increased taste and smell function. Unfortunately, clinical chemosensory tests do not accurately diagnose this type of complaint. Yet, in the research setting, clinical tests may prove useful in clarifying the physiology behind the loss of taste and smell function observed in cancer patients. The fact that the majority of patients had difficulty identifying odours, could not accurately perceive chemosensory capability, and did not have cancer that would directly affect taste or smell receptors or any recent chemotherapy would point to a neural mechanism for chemosensory alterations in this study population. We suspect that this altered perception of taste and smell function is likely the result of a disturbance in sensory signal transduction. One theory to explain these results is that connections are disrupted during the regeneration of taste cells and nerve fibres after damage by cancer and/or treatment resulting in altered coding of chemical stimuli (9).

There are many factors that may contribute to a decline in taste and smell function of advanced cancer patients which include inflammation (10), previous chemotherapy or radiation treatment (11), medications (10) and age (6). Patients in this study did not have cancer or radiation treatment that would directly affect taste or smell receptors and had not had any recent chemotherapy. In addition, changes in smell function could not be explained by age alone when results were compared to normative data. Advanced cancer

patients are a diverse group with a variety of cancer types, treatments, and demographics. It is likely a combination of factors that result in the chemosensory alterations observed in this study, which may differ for each individual. More research is needed to determine the true origins of taste and smell changes in advanced cancer patients.

One challenge encountered in this research was the small sample size, with only 31 patients consenting to participate in the chemosensory study. Recruitment was difficult for this study as most advanced cancer patients are nearing the end of life and were unable to commit to the time needed to complete our study requirements. We recruited patients from the community, many of whom were approached for a number of other research studies. With a small sample size we are unable to control for many factors that affect chemosensory function including age, gender, smoking history, previous cancer treatment, and medications. Although the small sample size limits the statistical analysis and significant results described in this thesis, many interesting observations are revealed. Differences between patients reporting "stronger", "as strong", or "weaker" chemosensory function were not clear in this study however trends in the data warrant further research. We may see some of the patterns or trends observed in this study become statistically significant results with a larger sample size.

**Are Liquid Nutritional Supplements Appropriate for Advanced Cancer Patients?**

We related dietary patterns of advanced cancer patients to concurrent pain and symptom profiles, with specific attention to chemosensory function. Three dietary patterns characterized by meat/dessert, fruit/pasta, and liquid/supplement were consumed by 65%,

23%, and 12% of the advanced cancer population studied respectively. These patterns are similar to those identified in our earlier work (12). A large proportion of advanced cancer patients (88%) followed dietary patterns based on normal foods such as meats, desserts, and fruit. However, a small but important group of patients (12%) consume a largely liquid diet based on nutritional supplements.

Patients who belonged to the liquid/supplement pattern consumed 29% of calories from oral nutritional supplements and a further 13% of calories overall from soups and milk. Patients consuming this liquid diet have greater chemosensory alterations, lower nutrient intakes, higher symptom distress, and are closer to death. When patients were grouped based on their perception of chemosensory function there was a trend toward lower calorie and protein intake in patients reporting both a "stronger" and a "weaker" perception of the chemical senses. Therefore, it appears that chemosensory alterations, regardless of the nature of dysfunction, contribute to poor dietary intake. It seems that taste and smell changes together with a high symptom burden contribute to the poor dietary intake and reliance on liquid nutrition in this group of advanced cancer patients.

A reliance on liquid nutritional supplements appears to be a result of the high symptom burden associated with the end of life. Nutritional supplements are promoted to add to oral food intake in order to increase overall dietary intake. The results from this study suggest that nutritional supplement use at the end of life does not result in an adequate intake of calories or protein (13). Studies have shown that patients may not increase dietary intake with nutritional supplements, but rather replace habitual food intake

(14,15). Therefore, promoting nutritional supplements in advanced cancer patients may not result in the intended increase in nutritional intake for all users and may instead replace usual food intake at the expense of social and quality of life aspects such as food enjoyment and family meal consumption.

In this study, high users of nutritional supplements were patients with severe chemosensory complaints. These patients often complain of an increased sensitivity to odours and tastes (1). It is essential to consider the unique taste perception and preferences of advanced cancer patients during product development bearing in mind that patients with chemosensory disorders are key consumers of nutritional supplements. Hedonic judgements measure acceptability or pleasantness and can be used to determine taste and flavour preferences of advanced cancer patients. Careful consideration of flavour, smell, mouth-feel and volume of a new nutritional supplement for advanced cancer patients can improve adherence and intake (15).

Finally, it is worth considering whether it is appropriate to push nutritional interventions such as oral nutritional supplements for advanced cancer patients at the end of life. Previous studies and anecdotal reports of participants in this research indicate that many patients accept a loss of appetite and poor food intake as a natural consequence of approaching the end of life (16-18). At this point, it may be beneficial to work with the family and/or caregiver, who have more difficulty accepting appetite loss, to understand the physiology of dying. Each patient should be assessed individually to determine their views on an appropriate course of nutrition support.

**Future Topics of Investigation**

The taste and smell survey used in this research begins to elucidate the impact of chemosensory alterations on quality of life. The next step for further research is a qualitative study to clarify the impact of taste and smell disorders on daily living for cancer patients at the end of life. Interviews with individual patients could be used to determine the impact of taste and smell changes on QOL and the stategies patients use to overcome this bothersome symptom.

Continued chemosensory research using the same comprehensive study design will help to confirm the initial observations reported in this thesis. However, this research captures only a "snapshot" of chemosensory function in advanced cancer patents at one point in time. Another area of research would be a longitudinal study following patients throughout the disease trajectory to determine the timeline around the loss, recovery, and/or alteration in taste and smell function that results from cancer and its treatments.

Finally, more research is needed to develop food products and/or nutritional supplements that appeal to cancer patients experiencing altered taste and smell function. We must also consider the appropriateness of recommending commercial nutritional supplements in terms of palatability and effectiveness during end of life care.

**Final Comments**

The results presented here expand the current knowledge of chemosensory dysfunction in advanced cancer patients. This is the first study using a multi-dimensional research

approach combining self-assessed patient perception with clinical test procedures which begins to clarify how taste and smell function is affected in advanced cancer. Taste and smell alterations are important and prevalent symptoms of cancer that deserve more attention in oncology research and clinical oncology management. Patients are commonly asked to rate symptoms such as pain and nausea; we suggest that patient perception of taste and smell is an important assessment lacking in current cancer care.

The perception of chemosensory function is materially different than the olfaction and gustation quantified by clinical tests. In the research setting, clinical chemosensory tests may help to clarify the physiology behind the loss of taste and smell function seen in cancer patients. However, the common complaint of advanced cancer patients is a perception of altered and/or increased taste and smell function. A subjective taste and smell questionnaire is fast and low-burden tool to identify taste and smell alterations in the clinical setting. Results of the taste and smell survey reveal an association between the perception of chemosensory changes and low food intake – including a reliance on liquid nutrition, poor QOL, and high symptom burden.

Currently there are limited treatment options for cancer patients experiencing taste and smell changes. Further research is needed to develop interventions and food products that appeal to patients experiencing altered taste and smell function. An individualized approach to management is needed to control the entire range of cancer symptoms, including chemosensory alterations, which negatively impact dietary intake and QOL.

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## Appendix A: TASTE AND SMELL SURVEY – PART A

Participant Number: _____ Date: ____/____/____(month/day/year)

The purpose of this survey is to see how cancer affects the senses of taste and smell. Please answer the following questions as best you can.

1. Have you noticed any changes in your sense of taste? yes no

   If yes, please describe:

   _____

2. Have you noticed any changes in your sense of smell? yes no

   If yes, please describe:

   _____

3. Have you ever noticed that a food tastes different than it used to? yes no

   If yes, please describe:

   _____

4. Have you ever noticed that a food smells different than it used to? yes no

   If yes, please describe:

   _____

5. I have a persistent bad taste in my mouth (circle BEST answer)
   1. never
   2. rarely
   3. sometimes
   4. often
   5. always

6. The persistent taste is (circle ALL that apply)
   1. salty
   2. sweet (like sugar)
   3. sour (like lemon or vinegar)
   4. bitter (like black coffee or tonic water)
   5. other (specify) _____

7. Do specific drugs interfere with your sense of taste? yes no

   If yes, which ones?

   _____

8. Do some drugs taste worse than others? yes no

   If yes, which ones?

   _____

9. Do specific drugs interfere with your sense of smell? yes no

   If yes, which ones?

   _____

10. Do some drugs smell worse than others? yes no

    If yes, which ones?

    _____

11. Comparing my sense of taste now to the way it was before I was diagnosed with cancer:

    a. Salt tastes (circle BEST answer)
       1) stronger
       2) as strong
       3) weaker
       4) I cannot taste it at all

    b. Sweet (sugar) tastes (circle BEST answer)
       1) stronger
       2) as strong
       3) weaker
       4) I cannot taste it at all

    c. Sour (lemon or vinegar) tastes (circle BEST answer)
       1) stronger
       2) as strong
       3) weaker
       4) I cannot taste it at all

d. Bitter (black coffee or tonic water) tastes (circle BEST answer)

1) stronger
2) as strong
3) weaker
4) I cannot taste it at all

12. Comparing my sense of smell now to the way it was before I was diagnosed with cancer,
odors are

1) stronger
2) as strong
3) weaker
4) I cannot smell at all

13. Over the past 3 months, I would rate my abnormal sense of taste as: (circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

14. How has your abnormal sense of taste affected your quality of life?

_____

_____

15. Over the past 3 months, I would rate my abnormal sense of smell as: (circle BEST answer)

1. insignificant
2. mild
3. moderate
4. severe
5. incapacitating

16. How has your abnormal sense of smell affected your quality of life?

_____

_____

## Appendix B: TASTE AND SMELL SURVEY – PART B

Participant Number: _____ Date: ____/____/____(month/day/year)

The purpose of this part of the survey is to determine if there are factors other than cancer that influence your sense of taste and smell. Please answer the following questions as best you can.

| | | |
|---|---|---|
| 1. Do you wear dentures? | Yes | No |
| 2. Have you had mouth and/or gum infections in the past two years? | Yes | No |
| 3. Are you currently bothered by hay fever and/or allergies? | Yes | No |
| 4. Are you currently bothered by your sinuses? | Yes | No |
| 5. Does your sense of smell change from day to day? | Yes | No |
| 6. Does your sense of taste change from day to day? | Yes | No |
| 7. Has a doctor previously diagnosed you with any taste or smell problems? | Yes | No |
| 8. Before your cancer, did you have any problems with your sense of taste or smell? | Yes | No |
| 9. Do you smell "phantom odours"? (you can smell something but the source of the smell is nowhere near you) | Yes | No |
| 10. Are you currently a smoker? | Yes | No |
| 11. If you are not a current smoker, are you a former smoker? | Yes | No |
| 12. Does a caregiver prepare the majority of your meals? | Yes | No |
| 13. Do you prepare the majority of your meals? | Yes | No |
| 14. Do you eat your meals alone? | Yes | No |

Some symptoms or problems can affect your ability to eat. Please indicate the extent to which you experienced these symptoms or problems in the past week, using a scale from one to five, where 1 represents "not at all" and 5 represents "very often"

| | Not at all | | | | Very often |
|---|---|---|---|---|---|
| 15. Do you have pain or soreness in your mouth? | 1 | 2 | 3 | 4 | 5 |
| 16. Do you have pain in your jaw? | 1 | 2 | 3 | 4 | 5 |
| 17. Do you have pain in your throat? | 1 | 2 | 3 | 4 | 5 |
| 18. Do you have problems swallowing liquids | 1 | 2 | 3 | 4 | 5 |
| 19. Do you have problems swallowing pureed foods? e.g. applesauce | 1 | 2 | 3 | 4 | 5 |
| 20. Do you have problems swallowing solid foods? | 1 | 2 | 3 | 4 | 5 |
| 21. Do you have a dry mouth? | 1 | 2 | 3 | 4 | 5 |
| 22. Do you have sticky saliva? | 1 | 2 | 3 | 4 | 5 |
| 23. Do you have trouble eating? | 1 | 2 | 3 | 4 | 5 |
| 24. Do you suffer from constipation? | 1 | 2 | 3 | 4 | 5 |
| 25. Do you enjoy your meals? | 1 | 2 | 3 | 4 | 5 |
| 26. Do you feel hungry at mealtime? | 1 | 2 | 3 | 4 | 5 |

## Appendix C: Functional Assessment of Anorexia/Cachexia Therapy (FAACT)

Below is a list of statements that other people with your illness have said are important. **By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.**

| PHYSICAL WELL-BEING | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| I have lack of energy | 0 | 1 | 2 | 3 | 4 |
| I have nausea | 0 | 1 | 2 | 3 | 4 |
| Because of my physical condition, I have trouble meeting the needs of my family | 0 | 1 | 2 | 3 | 4 |
| I have pain | 0 | 1 | 2 | 3 | 4 |
| I am bothered by side effects of treatment | 0 | 1 | 2 | 3 | 4 |
| I feel ill | 0 | 1 | 2 | 3 | 4 |
| I am forced to spend time in bed | 0 | 1 | 2 | 3 | 4 |

| SOCIAL/FAMILY WELL-BEING | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| I feel close to my friends | 0 | 1 | 2 | 3 | 4 |
| I get emotional support from my family | 0 | 1 | 2 | 3 | 4 |
| I get support from my friends | 0 | 1 | 2 | 3 | 4 |
| My family has accepted my illness | 0 | 1 | 2 | 3 | 4 |
| I am satisfied with family communication about my illness | 0 | 1 | 2 | 3 | 4 |
| I feel close to my partner (or the person who is my main support) | 0 | 1 | 2 | 3 | 4 |

Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please check this box and go to the next section ☐

| | | | | | |
|---|---|---|---|---|---|
| I am satisfied with my sex life | 0 | 1 | 2 | 3 | 4 |

**By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.**

| EMOTIONAL WELL-BEING | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| I feel sad | 0 | 1 | 2 | 3 | 4 |
| I am satisfied with how I am coping with my illness | 0 | 1 | 2 | 3 | 4 |
| I am losing hope in the fight against my illness | 0 | 1 | 2 | 3 | 4 |
| I feel nervous | 0 | 1 | 2 | 3 | 4 |
| I worry about dying | 0 | 1 | 2 | 3 | 4 |
| I worry that my condition will get worse | 0 | 1 | 2 | 3 | 4 |

| FUNCTIONAL WELL-BEING | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| I am able to work (include work at home) | 0 | 1 | 2 | 3 | 4 |
| My work (include work at home) is fulfilling | 0 | 1 | 2 | 3 | 4 |
| I am able to enjoy life | 0 | 1 | 2 | 3 | 4 |
| I have accepted my illness | 0 | 1 | 2 | 3 | 4 |
| I am sleeping well | 0 | 1 | 2 | 3 | 4 |
| I am enjoying the things I usually do for fun | 0 | 1 | 2 | 3 | 4 |
| I am content with the quality of my life right now | 0 | 1 | 2 | 3 | 4 |

**By circling one (1) number per line, please indicate how true each statement has been for you <u>during the past 7 days</u>.**

| ADDITIONAL CONCERNS | Not at all | A little bit | Somewhat | Quite a bit | Very much |
|---|---|---|---|---|---|
| I have a good appetite | 0 | 1 | 2 | 3 | 4 |
| The amount I eat is sufficient to meet my needs | 0 | 1 | 2 | 3 | 4 |
| I am worried about my weight | 0 | 1 | 2 | 3 | 4 |
| Most food tastes unpleasant to me | 0 | 1 | 2 | 3 | 4 |
| I am concerned about how thin I look | 0 | 1 | 2 | 3 | 4 |
| My interest in food drops as soon as I try to eat | 0 | 1 | 2 | 3 | 4 |
| I have difficulty eating rich or "heavy" foods | 0 | 1 | 2 | 3 | 4 |
| My family or friends are pressuring me to eat | 0 | 1 | 2 | 3 | 4 |
| I have been vomiting | 0 | 1 | 2 | 3 | 4 |
| When I eat, I seem to get full quickly | 0 | 1 | 2 | 3 | 4 |
| I have pain in my stomach area | 0 | 1 | 2 | 3 | 4 |
| My general health is improving | 0 | 1 | 2 | 3 | 4 |

## Appendix D: Edmonton Symptom Assessment System (ESAS)

Participant Number: _____ Date: ____/____/____(month/day/year)

**Please circle the number that best describes:**

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| No pain | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible pain |
| Not tired | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible tiredness |
| Not nauseated | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible nausea |
| Not depressed | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible depression |
| Not anxious | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible anxiety |
| Not drowsy | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible drowsiness |
| Best appetite | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible appetite |
| Best feeling of wellbeing | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible feeling of wellbeing |
| No shortness of breath | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | Worst possible shortness of breath |
| Other problem | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | |

## Appendix E: Patient Generated Subjective Global Assessment (PGSGA)

**Nutritional Health Assessment**

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**Name:** _____
**ID:** _____
**Age:** _____
**Date:** _____

**History (Boxes 1-4 are designed to be completed by the patient)**

**1. Weight:**
In **summary of my current and recent weight**

My height is about _____ feet/inches tall
(or _____ cm)

My current weight is about _____ pounds
(or _____ kg)
One month ago I weighed about _____ pounds
(or _____ kg)
Six months ago I weighed about _____ pounds
(or _____ kg)

During the past two weeks my weight has:
☐ decreased
☐ not changed
☐ increased

**2. Food Intake**
As compared to my normal intake, I would **rate the QUANTITY of my food intake during the past month** as:

☐ unchanged
☐ more than usual
☐ less than usual

**I am not taking food of the following TYPE:**
☐ *normal food* in my normal amount
☐ *normal food* but less than usual
☐ little solid food
☐ only liquids
☐ only nutritional supplements
☐ very little of anything
☐ only tube feedings or only nutrition by vein

**3. Symptoms:** I have had the following problems that **have kept me from eating enough** during the past two weeks (check all that apply):
☐ no problems eating
☐ no appetite, just did not feel like eating
☐ nausea ☐ vomiting
☐ consitipation ☐ diarrhea
☐ mouth sores ☐ dry mouth
☐ things taste funny or have no taste
☐ smells bother me
☐ problems swallowing
☐ dental problems
☐ feel full quickly
☐ pain; where? _____
☐ other* _____
* Example: depression, money

**4. Activities and Function:**
Over the **past month, I would generally rate my ACTIVITY** as:

☐ normal with no limitations
☐ not my normal self, but able to be up and about with fairly normal activity
☐ not feeling up to most things, but in bed or chair less than half the day
☐ able to do little activity and spend most of the day in bed or chair
☐ pretty much bed ridden rarely out of bed

**Information provided by:** ☐ Patient ☐ Family Member
**Signature:** _____ **Date:** _____

## Appendix F: Taste and Smell Profile

| | |
|---|---|
| Gender:<br>Age:<br>Dx: | Height: Weight:<br>BMI: 6 month wt loss: |
| **Food Intake:**<br>Energy: ____ kcal/day<br>____ kcal/kg/day<br>___ meets recommendations<br>___ below recommendations | Protein: ____ g/day<br>____ g/kg/day<br>___ meets recommendations<br>___ below recommendations |
| **Taste and Smell Survey:**<br>___ Insignificant<br>___ Mild<br>___ Moderate<br>___ Severe | Sweet tastes: _ stronger_as strong_weaker<br>Salt tastes: _ stronger_as strong_weaker<br>Sour tastes: _ stronger_as strong_weaker<br>Bitter tastes: _ stronger_as strong_weaker<br>Odours smell: _stronger_as strong_weaker |
| **Taste Detection Thresholds:**<br>Sweet: __ Normal sensitivity<br>__ Low sensitivity<br>Salt: __ Normal sensitivity<br>__ Low sensitivity | Sour: __ Normal sensitivity<br>__ Low sensitivity<br>Bitter: __ Normal sensitivity<br>__ Low sensitivity |
| **Smell Function:**<br>Odour Identification:<br>___ Normosmia<br>___ Mild__Moderate__Severe Microsmia<br>___ Anosmia<br>___ percentile for age group | Odour Threshold:<br>___ Normosmia<br>___ Hyposmia<br>___ Anosmia<br>___ percentile for age group |
| **Quality of Life:**<br>____ above average ____ below average | FAACT Score: /156 |
| **Symptom Burden:**<br>ESAS (out of 10):<br>___ Pain<br>___ Tired<br>___ Nausea<br>___ Depression<br>___ Anxiety<br>___ Drowsy<br>___ Appetite<br>___ Feeling of wellbeing<br>___ Shortness of breath | PGSGA:<br>__ No appetite __ Vomiting<br>__ Nausea __ Diarrhea<br>__ Constipation __ Dry mouth<br>__ Mouth sores __ Pain<br>__ Dental problems __ Feel full quickly<br>__ Problems swallowing<br>__ Smells bother me<br>__ Things taste funny or have no taste |